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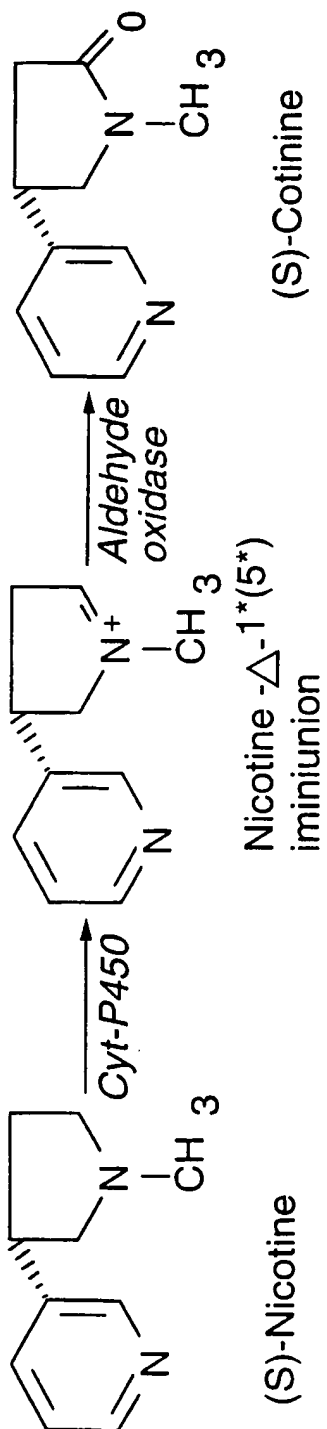


FIG.1

FIG.2A

LOCUS HSU22027 7215 bp DNA PRI 22-OCT-1995
 DEFINITION Human cytochrome P450 (CYP2A6V2) gene, complete cds.
 ACCESSION U22027
 NID g1008461
 KEYWORDS
 SOURCE human.
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 REFERENCE 1 (bases 1 to 7215)
 AUTHORS Fernandez-Salguero,P., Hoffman,S.M., Cholerton,S.,Mohrenweiser,H.,
 Raunio,H., Rautio,A., Pelkonen,O., Huang, J.D., Evans, W.E.,
 Idle, J.R. et,al.
 TITLE A genetic polymorphism in coumarin 7-hydroxylation: sequence of the
 human CYP2A genes and identification of variant CYP2A6 alleles
 JOURNAL Am. J. Hum. Genet. 57 (3), 651-660 (1995)
 MEDLINE 95397851
 REFERENCE 2 (bases 1 to 7215)
 AUTHORS Fernandez-Salguero,P.
 TITLE Direct Submission
 JOURNAL Submitted (01-MAR-1995) Pedro Fernandez-Salguero, National
 Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20894, USA
 FEATURES Location/Qualifiers
 source 1..7215
 /organism="Homo sapiens"

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FIG.2A CONT.

5'UTR

CDS

```

782..790
join (791..970, 1237..1399, 2115..2264, 2499..2659,
3207..3383, 4257..4398,4873..5060,5577..5718, 6308..6489)
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/codon_start=1
/product=cytochrome P450"
/db_xref-PID:g1008462"
/translation=MLASGMLLVALLACLTVMLMSVWQQRKSKGKLPFGPTPLPFIG
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RSTHGANIDPTFFLSRSTVSNVISSIVFGDRFDYKDKEFLSLLRMMLGIFQFTSTSTGQ
LYEMFSSVMKHLPGPQQQAFQLLQGLEDFIAKKVEHNQRTLDPNSPRDFIDSLIRMQ
EEKNPNTEFYLNLMSTLNLFIAGTETVSTTLGYGFLLLMKHPEVEAKVHEEIDRV
IGKNRQPKFEDRAKMPYMEAVIHEIQRFQDVI PMSLARRVKKDTKFRDFFLPKGIEVF
PMLGSVLRDLRFFSNPRDFNPQHFLGKQGFKKRDVAFVPFSIRKRNCFGEGLARMELF
LFFTTVMQNFRLKSSQSPKDDIDVSPKHVGFATIPRNYTMSFLPR
791..970
/gene=CYP2A6V2:
/number=1
1237..1399
/gene=CYP2A6V2:
/number=2
2115..2264

```

exon

exon

exon

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FIG.2A CONT.

exon	/gene=CYP2A6V2: /number=3 2499..2659 /gene=CYP2A6V2: /number=4 3207..3383 /gene=CYP2A6V2: /number=5 4256..4398 /gene=CYP2A6V2: /number=6 4873..5060 /gene=CYP2A6V2: /number=7 5577..5718 /gene=CYP2A6V2: /number=8 6308..6489 /gene=CYP2A6V2: /number=9 6490..6744	1646 a	2196 c	1746 g	1627 t
3'UTR					
BASE COUNT					
ORIGIN					

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FIG.2A CONT.

BASE COUNT

```

1  aagttcccct gaaatatggc tctggtcttc ctccccttgc caatgaagaa gatggcagtg
61  gaggttctat ggcagccatc ctggcctcac tctgaggttc caatgaggat tctgggcatac
121 aagagacagc tctgggcaaa gctaaataca gtcagccctt ggaccagtg ctgggctgct
181 gggcttcttg ggagaagcc gctgggcttg ctacacactc ctctcccag aaactccaca
241 ccacagccc tgggtcttcc tagccccgag actttcaagt ccatatgcct ggaatcccc
301 ttccctgagac ccttaaccct gcatacctca caacagaaga ccctaaatg cacagccaca
361 ctttgtctta ccctaataaa accagacct ttggattcct ctcccctgga accccagat
421 ccgcacaact ttgggtgca ttctactct cagaccccaa atccaaagcc caagtgcctc
481 cctatgcaaa tattccaaac tcctcagttc tacagcttat ctgttgcccc ctctaaatc
541 cacagccctg cggcaccctt cctgaagtac cacagattta gtctggaggc cccctctctg
601 ttcagctgcc ctggggctcc ctatacctcc ctbgctggct gtgtcccaag ctaggcagga
661 ttcatggtgg ggcattgtagt tgggaggtga aatgaggtaa ttatgtaatc agccaaagtc
721 catccctctt ttccaggcag tataaaggca aaccacccca gccgtcacca tctatcatcc
781 ctctaccacc atgctggcct cagggatgct tctggtggcc ttgctggcct gcctgactgt
841 gatggtcttg atgtctgtt ggacagcagag gaagagcaag gggaagctgc ctccgggacc
901 caccatcttg cccttcattg gaaactacct gcagctgaac acagagcaga tgtacaactc
961 cctcatgaag gtgtcccaag acagggagat ggggtgtctcg gggtgggggc tgcctagtgt
1021 gctggggctt tgtggcaggg ggttgaccag tgtggaccag agtcttagga aatggagtgt
1081 tggagtctca gcatcagaaa gacaggatct tgggatgtcc agtccctga ctgtgagaac
1141 ctgggtgcga agcatcccag cacatgacat ctcggtgctg ggccccattc agagtggagg
1201 gttctccctc taaccactcc caccacctc catcagatca gtgagcgcta tggccccgtg
1261 ttcaccattc acttggggcc cggcggtgtc gtggtgtgtg gtggacatga tgccgtcagg

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FIG.2A CONT.

1321 gaggctctgg tggaccaggc tgaggagttc agcgggagc gcgagcaagc caccttcgac
 1381 tgggtcttca aaggctatgg tgcccaagag ggggaaggtg ggcaggtgga cacgaaggtc
 1441 tcagtgttcc cagccttctc cctgactctc ctgacaaactg gaggataaagg gagagtcccc
 1501 agtctgggtc tccctcccca tctccctaca ttggggcctc tccatgtgta tccctcacct
 1561 gtctccagcg gccctgtcct gattcctccc tgccctctctc tgccccacct ccttattctc
 1621 tctcactgga gtctcctctt tccctctct tccctctctc ctccatctct tgggtttctg
 1681 ttaccagcc ctgggtctct gtctacatga gtctttgagg cctctcttagc ttctgggctt
 1741 ctctgggttt ctcatctctc cggatccctt tctcaattct tctctctgtct taggatgcca
 1801 gggttattcc tacttccaca tcttcaggct ccattctctg gtaacagtct ctcttccttc
 1861 cagaccctct ctgtttctat ctcaatatta aactctctgc tccagctcag cttaagaatc
 1921 tcacaccaag agaggatgtc ctccaccag atctcccat atctcactac cccacctcc
 1981 atcctctgcc tccatcactc tctttctctc cccactgccc tgcggacgag atccaatgga
 2041 gtgtggagct aatgccgtga agctatgtgc atctctctgt ctggccgtac ctgggtaata
 2101 acctgatcga ctaggcgtgg tattcagcaa cggggagcgc gccaaagcag tcctgcgctt
 2161 tgccatcgcc acctgaggg acttcggggt gggaagcga ggcatcgagg agcgatcca
 2221 ggaggagtcg ggcttctca tcgaggccat ccggagcacg cagggtgagc aggggacccc
 2281 gagtgcgggg gcaggagaag gaaaacaccc aggacgagga accgcgcgc gtctgcctg
 2341 gggatgggga ctagggtggg aaaggcgccc gcacttccag ccttgagtc tggcgctggg
 2401 aatttggctc aacaaggccc tgcctcctgg aattctgact ctctcagac ctctgagttg
 2461 actctctccc caaccctt ctcccacat acccgaggc gccaatatcg atcccacct
 2521 ctctctgagc cgcacagtct ccaatgtcat cagctccatt gtctttgggg accgctttga
 2581 ctataaggac aaagagtctc tgtcactgtt gcgcatgatg ctaggaaatct tccagttcac
 2641 gtcaacctcc acggggcagg taatggttgc agccccggcc gtgaaggccc ttacccaaac

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FIG.2A CONT.

```

2701 cggcaaatg ttccctacc ggggaaggg ggcccaaat tccaccgcc cccggacag
2761 tgtccctca aatcagtc cggatttggg caaatggca gagtgaacc agaccgggt
2821 tggttgtcca atccctgct ctccaggac accgggatac cacaacagat gctcccaaa
2881 acagagcctg ctggcaggat gcataccctc agctcagctc tctcaccctg ggcacgtgtt
2941 ccatcccca acttaccggt aatttctaac agatgctccc taccaggctc ttcttgaata
3001 ttttaacacc cggaaaccct gggtacctaa cttcctgt aaactttaga gattagtctc
3061 tatccggccc ctctgaata cctaaccacc ggagaccaga tgcctttaa ttagttcctt
3121 ccttgctatg aaacaaatcc cattcccatc agctcctgcc ccgtgacagc tgtccttccc
3181 ttcccatcct ctctctgcaa cccagctct atgagatgtt ctcttcggtg atgaaacacc
3241 tgccaggacc gcagcaacag gccttctcagt tgctgcaagg gctggaggac ttcatagcca
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3361 cctttctcat ccgcatgcag gaggtacacc ccagcagcca ctgcggggag atgcaaaagcc
3241 aggcagaggg aaatcagtct gggagtgggg caggcagatg acacaggccc attcaaatca
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3601 gccaacatgg tcaaaccccg tctctactaa aaatccaaaa attagtggg catggtggcg
3661 cgaagggggg cagaggttgc aatgagccaa gatcacggca ttgcactcca gtctgggtga
3721 cagaatgagg ccctgtgtca aaaaaatta atcacttgtt taaaaagtaa gtgagcctgc
3781 atggtcatgc gcatgtgtag ctccagctac tcaggaggct gaggtggag gattgcttga
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3901 aaaaaacaaa aaaaagctg acagctaagt tgataattga cggacagatg gtcagcaagg
3961 taacgaaggt gagaagggaag agcattgggg gcaacgccag gagtacgggc aagggtggt

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FIG.2A CONT.

```

4021 tcctagagcg agtctggtag gatctagggc ccctcttctc caccctgagg tcttgcccca
4081 aagagaggtc gaggtgctg ggattgcgct agactcgagt ctgtgtagat cttgggggtcc
4141 cctcttgacc ccattggctc tgaacctaaag agtgggaagat ccatgggggtg aacccttaga
4201 tggtgccctg aggtcaagca ggagtgggt tgtcctaaag cccctctcc cttcaggagg
4261 agaagaacc caacacggag ttctacttga agaacctgat gatgagcagc ttgaacctct
4321 tcattgcagg caccgagacg gtcagacca ccctgcacta tggcttctta ctgctcatga
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4501 gtgacttgct gtccagagac agggcaacat tcagctggta ggcatcagct gagtctcatt
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4861 ctccctcccc agccaaggct catgaggaga ttgacagagt gatcggcaag aaccggcagc
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4981 gatttggaga cgtgatcccc atgagtctgg ccgcagagt caaaaaggac accaagtctc
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5161 ccctcaatca gtcaaaaaag acttcccca ccaccatc cgttccacct ttccacttag
5221 acactcctga gtcctgcac tctccagact ctttgtgtca ggagaatcaa acacatgttc
5281 ccaacttcc tatcttaaga aacagaagcc cccttccat tcggcctttt gtcataggga
5341 cagaaatctc aggtccccc aactcctgcc tagaaggaca tggaccccat gtctccaaa

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FIG.2A CONT.

5401 cttcctgttt cagagatgtg aaccttttat cccccaaggt cctccctcag aggtccccaa
 5461 ttcccatgcc tgccacttcc cctcacccgg gcacccctagt tccccctcca gcccctgtgt
 5521 actctcaaca atcccccaac ccgcctcatc acatacacct tcctcctccc tcccagggca
 5581 tagaagtgtt ccttatgttg ggtccgtgc tgagagacct caggttcttc tccaaccccc
 5641 gggacttcaa tccccagcac ttcctgggtg agaaggggca gtttaagaag cgtgatgctt
 5701 ttgtgccctt ctccatcagt aagagaccac tgtttggtgc caggcttact actcacacca
 5761 gcaggggcct ccttaacca cttccctct ctgccgtgta gcctagtatt tccccagctt
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 6241 tcggtactgg ggcgaggctg cactgagagt gggcttcacc tccacccctc ccgcctctcc
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 6361 tcaccaccg tcatgcagaa ctctcgccctc aagtcctccc agtcacctaag ggacattgac
 6421 gtgtccccc aacacgtggg ctttgccacg atccccgaa actacaccat gagcttcctg
 6481 ccccgctgag cgagggtgtt gccggtgaag gtctggtggg cggggccagg gaaagggcag
 6541 ggccaagacc gggcttggga gaggggcgca gctaaagactg ggggcaggat ggcggaaaag
 6601 aaggggcgtg gtggctagag ggaagagaag aaacagaagc ggctcagttc accttgataa
 6661 ggtgcttccg agctgggatg agaggaaagga aaccttaca ttatgctatg aagagtagta

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FIG.2A CONT.

6721 ataatagcag ctcttatttc ctgagcacgt acccccggtg cacctttggt caaaaacccat
6781 tgcacgctca cctaatttgc cacaaaaccc ccttcgaagg ggcgttcattg cccatttttac
6841 acgtgacaaa actgaggcctt agaaagtgtg ctctgatgtc tcacaaaaca taagtgcacca
6901 gaaaatctgc gaacacagat ctgtgccccat agccttctag acagattctt aaaaagcacc
6961 tattcctcac gcaaaacagt ttagtataga atcacatggc ctgaacatcc ctgtccgggg
7021 gaggttccca gagacctggg gggtaggttg cctgccttca ctgcacacat gccacactc
7081 tcacctactc aacatgctgt gactacccgg gtgtaaatctg tgcttgctac cagataaggc
7141 cactgtagcc cattcagagt cagcccaggg acacaacgag acatgactgg acatacaggg
7201 tcagtccatt aacaa

FIG.2B

LOCUS HSP452B6 1415 bp RNA 29-MAY-1992
 DEFINITION Human MRNA FOR CYTOCHROME P-450IIB6.
 ACCESSION X13494
 NID g35206
 KEYWORDS Cytochrome; cytochrome P450IIB6.
 SOURCE human.
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 REFERENCE 1 (bases 1 to 1415)
 AUTHORS Miles, J.S.
 TITLE Direct Submission
 JOURNAL Submitted (10-NOV-1988) Miles J.S., Imperial Cancer Research Fund,
 Lab of Molecular Pharmacology and Drug Metabolism, Hugh Robson
 Building, George Square, Edinburgh, EH8 9XD
 REFERENCE 2 (bases 1 to 1415)
 AUTHORS Miles, J.S., McLaren, A.Q. and Wolf, C.R.
 TITLE Alternative splicing in the human cytochrome P450IIB6 gene
 generates a high level of aberrant messages
 JOURNAL Nucleic Acids Res. 17 (20), 8241-8255 (1989)
 MEDLINE 90045947
 COMMENT The sequence is a compilation of genomic and cDNA clones. **map:
 chromosomal location=19q12-13.2;
 Data kindly reviewed (13-NOV-1989) by Miles, J.S.
 FEATURES Location/Qualifiers

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FIG.2B CONT.

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source      1..1415
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misc-feature 9..110
            /note=exon 1, partial"
misc-feature 111..273
            /note=exon 2"
misc-feature 274..423
            /note=exon 3"
misc-feature 424..584
            /note=exon 4"
misc-feature 585..761
            /note=exon 5"
misc-feature 762..903
            /note=exon 6"
misc-feature 904..1091
            /note=exon 7"
misc-feature 1092..1233
            /note=exon 8"
misc-feature 1234..1415
            /note=exon 9", coding region"
BASE COUNT   341 a   430 c   328 g   316 t
ORIGIN
1 gaattccgcc ctgcacccat gaccgcctcc caccagggcc cgcctctg ccccttttgg

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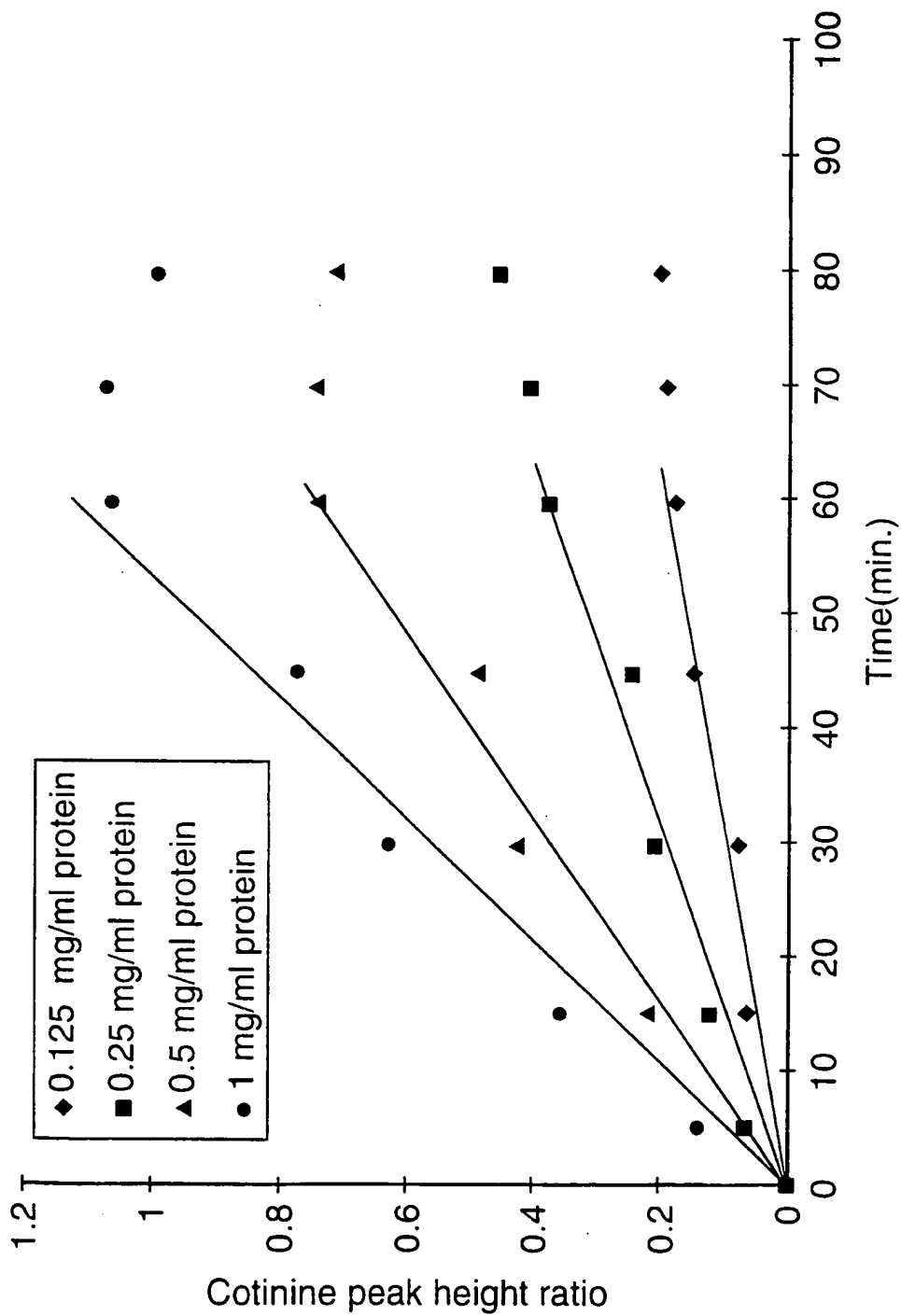
FIG.2B CONT.

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61 gaaaccttct gcagatggat agaagaggcc tactcaaatc ctttctgagg ttccgagaga
121 aatatgggga cgtcttcacg gtacacctgg gaccaggcc cgtggtcatg ctgtgtggag
181 tagaggccat acgggaggcc cttgtggaca agcctgaggc cttctctggc cggggaaaaa
241 tcgccatggg cgaccattc ttccggggat atggtgtgat ctttgccaat ggaaccgct
301 ggaagggtgct tcggcgattc tctgtgacca ctatgaggga cttcgggatg ggaagcggga
361 gtgtggagga gcggattcag gaggaggctc agtgtctgat agaggagctt cggaaatcca
421 agggggccct catggacccc accttctctt tccagtccat taccgccaac atcatctgct
481 ccacgtctct tggaaaacga ttccactacc aagatcaaga gttcctgaag atgctgaact
541 tgttctacca gactttttca ctcatcagct ctgtattcgg ccagctgttt gagctcttct
601 ctggcttctt gaaatacttt cctggggcac acaggcaagt ttacaaaaac ctgcaggaaa
661 tcaatgctta cattggccac agtgtggaga agcaccgtga aacctggac ccagcgccc
721 ccaaggacct catcgacacc tacctgtctc acatggaaaa agagaaatcc aacgcacaca
781 gtgaattcag ccaccagaac ctcaacctca acacgtctc gctcttctt gctggcactg
841 agaccaccag caccactctc cgctacggct tcctgctcat gctcaaataccctcatgttg
901 cagagagagt ctacagggag attgaaacagg tgattggccc acatcgccct ccagagcttc
961 atgaccgagc caaaatgcca tacacagagg cagtcatacta tgagattcag agattttccg
1021 accttctccc catgggtgtg cccacattg tcaccaaca caccagctc cgagggtaca
1081 tcatacccaa ggacacagaa gtatttttca tcctgagcac tgctctccat gaccacact
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1261 tcgcccagag ggaattgttc ctcttcttca ccaccatctt ccagaacttc tccatggcca
1321 gccccgtggc cccagaagac atcgatctga cccccagga gtgtggtgtg ggcaaaatatac
1381 ccccaacata ccagatccgc ttctgcccc gctga

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Protein-time curves of cotinine production from 100 μ M nicotine in the presence of 20 μ l rat cytosol by K20 human liver microsomes.

FIG.3

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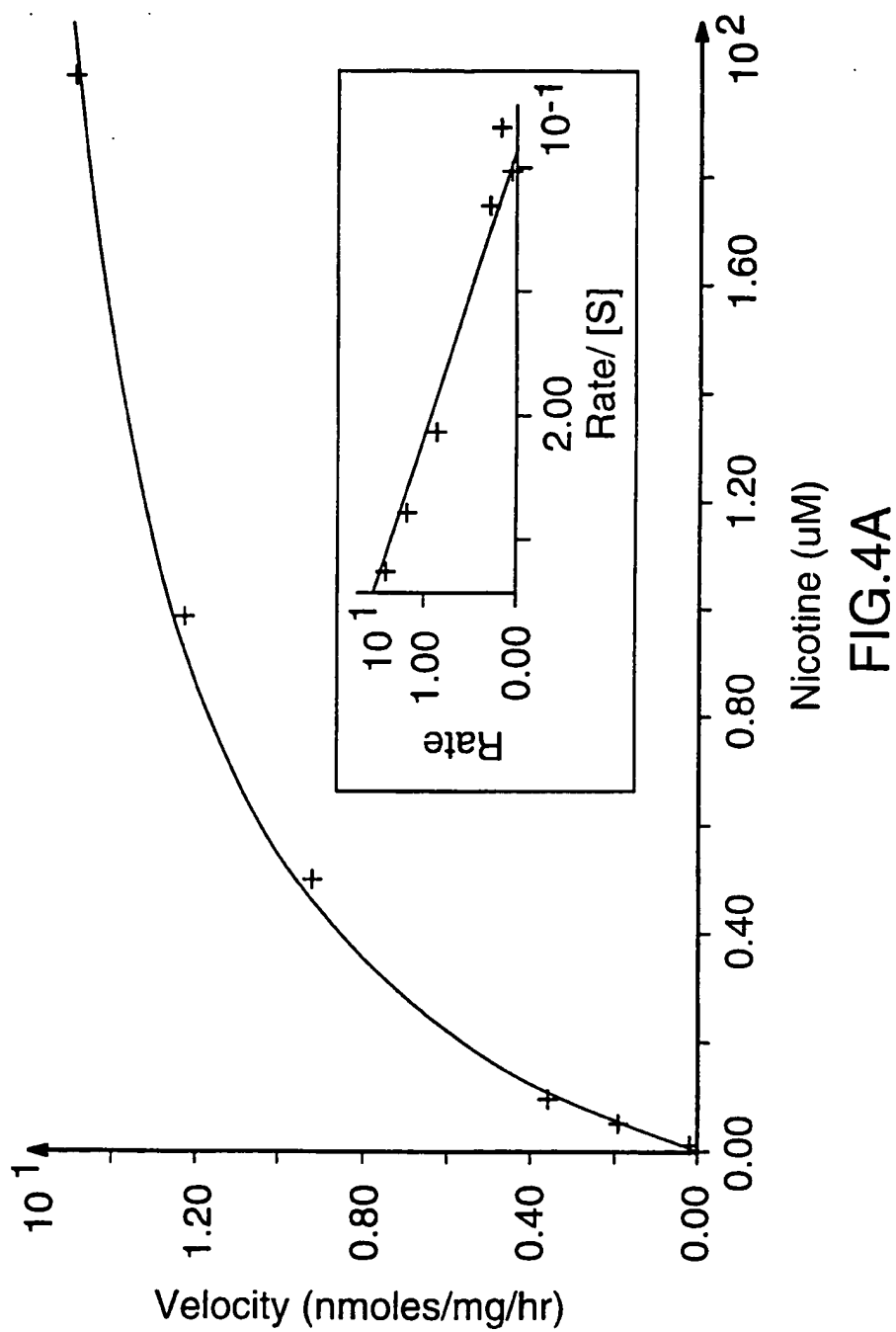


FIG.4A

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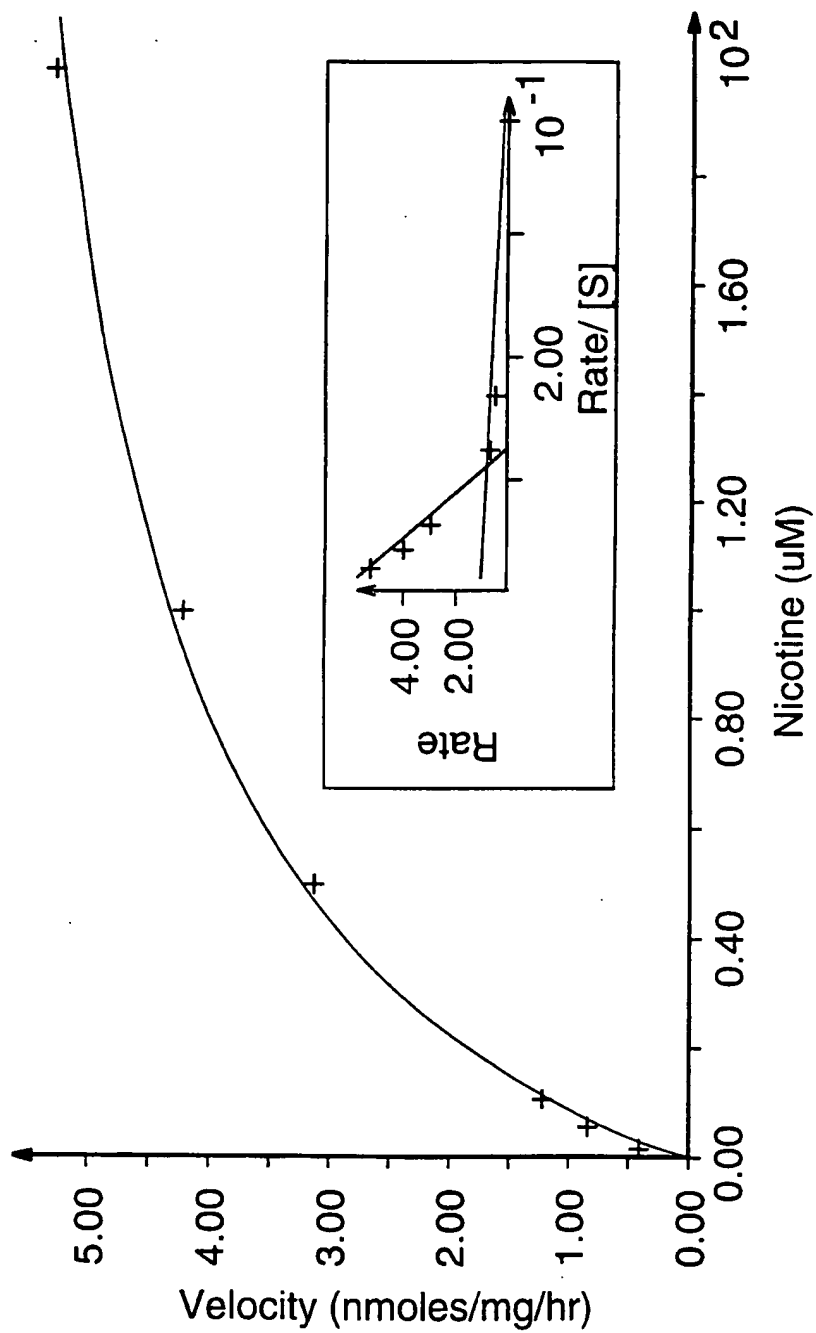
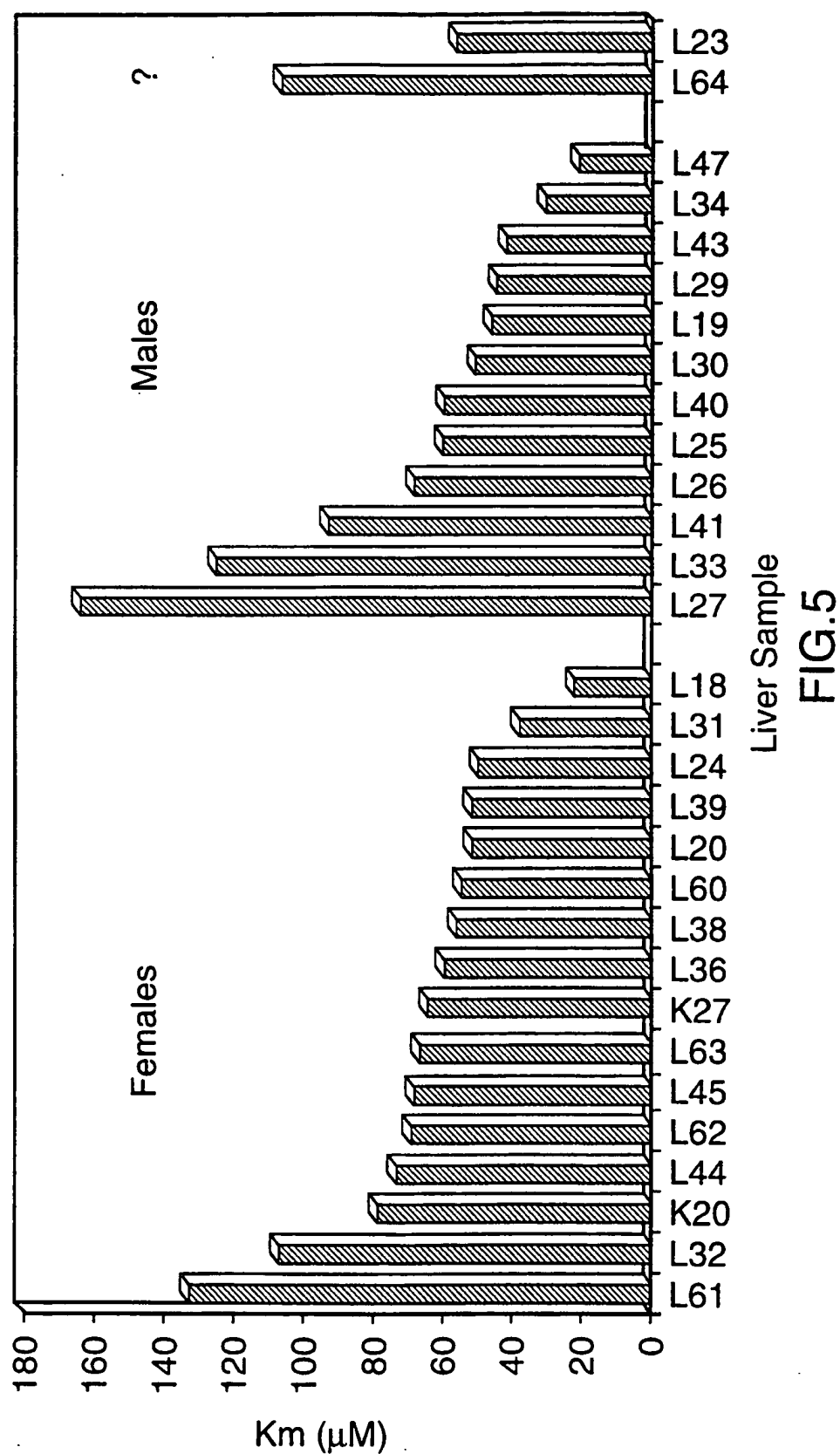


FIG. 4B

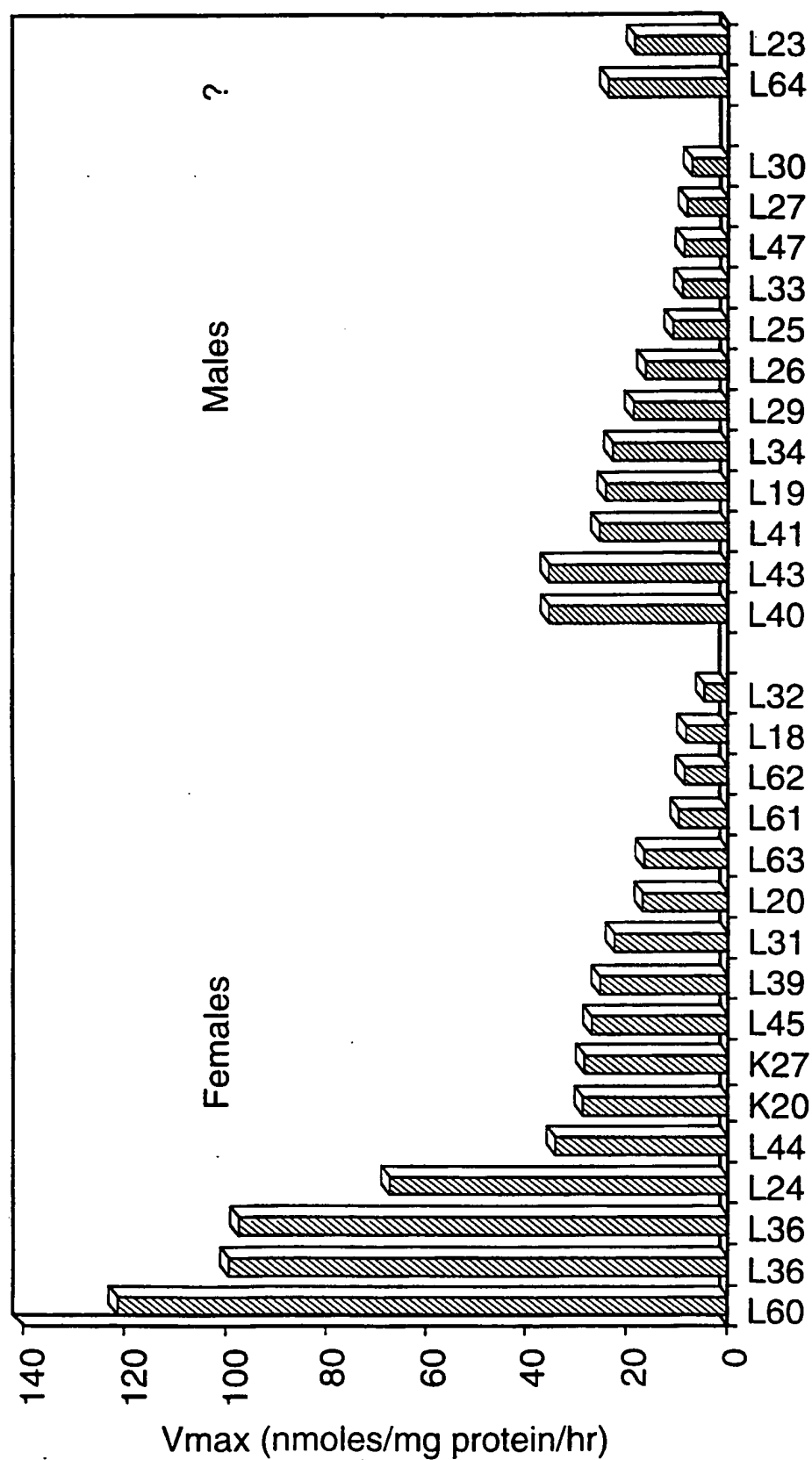
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Liver Sample

FIG.5

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Liver Sample
FIG.6

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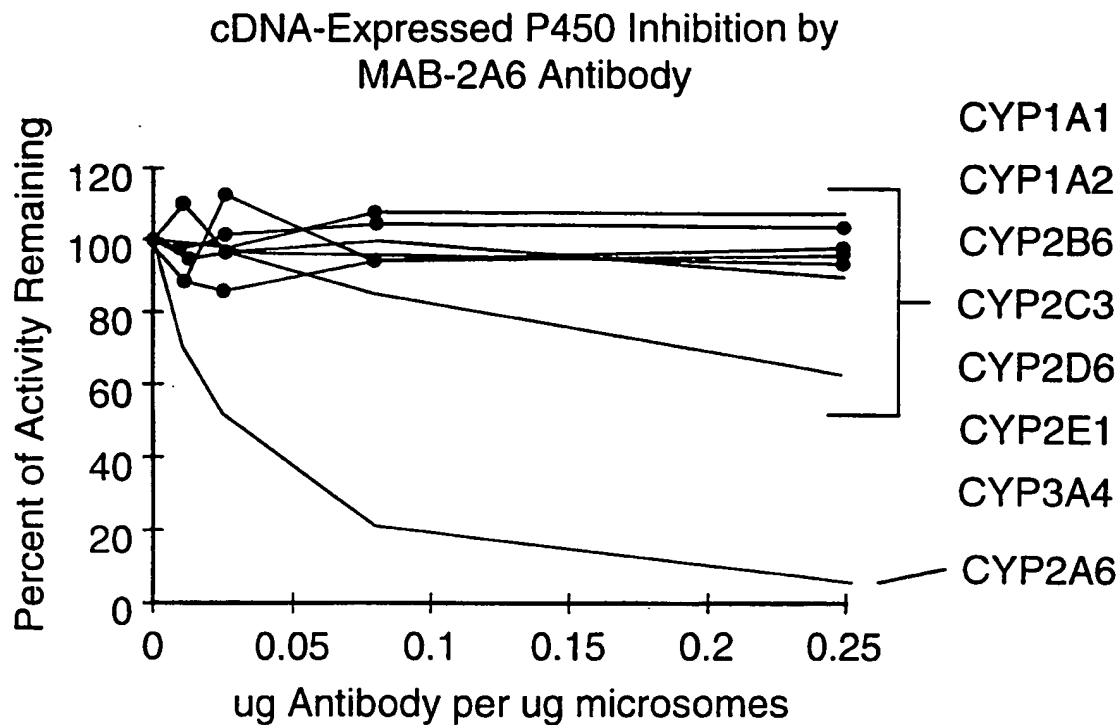


FIG.7A

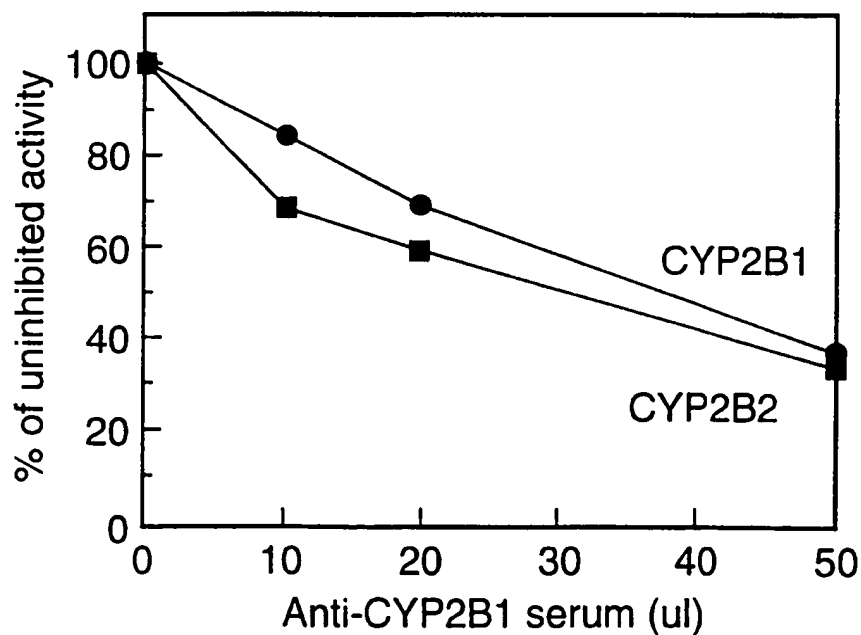


FIG.7B

BEST AVAILABLE COPY

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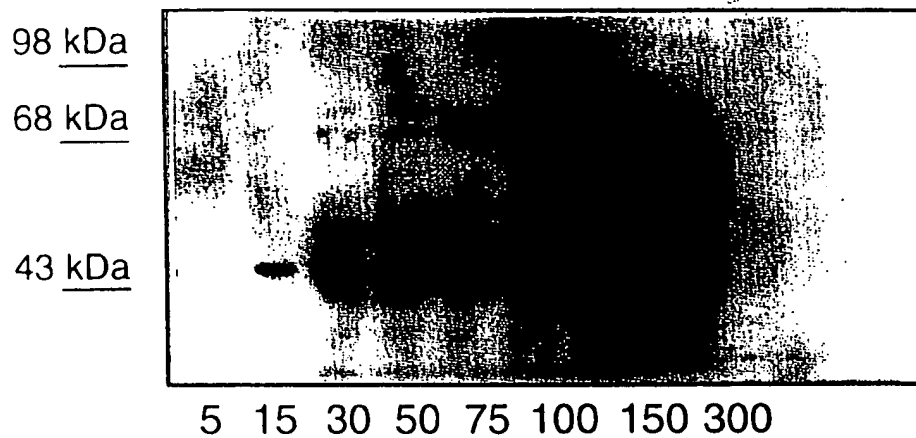


FIG.8A

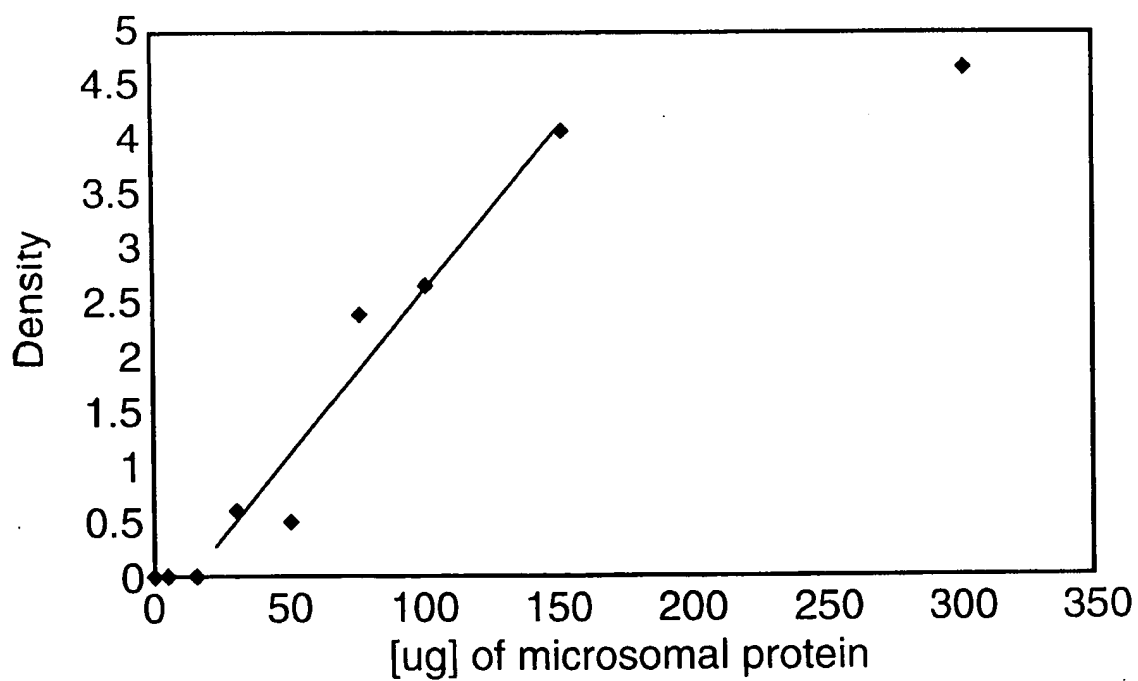
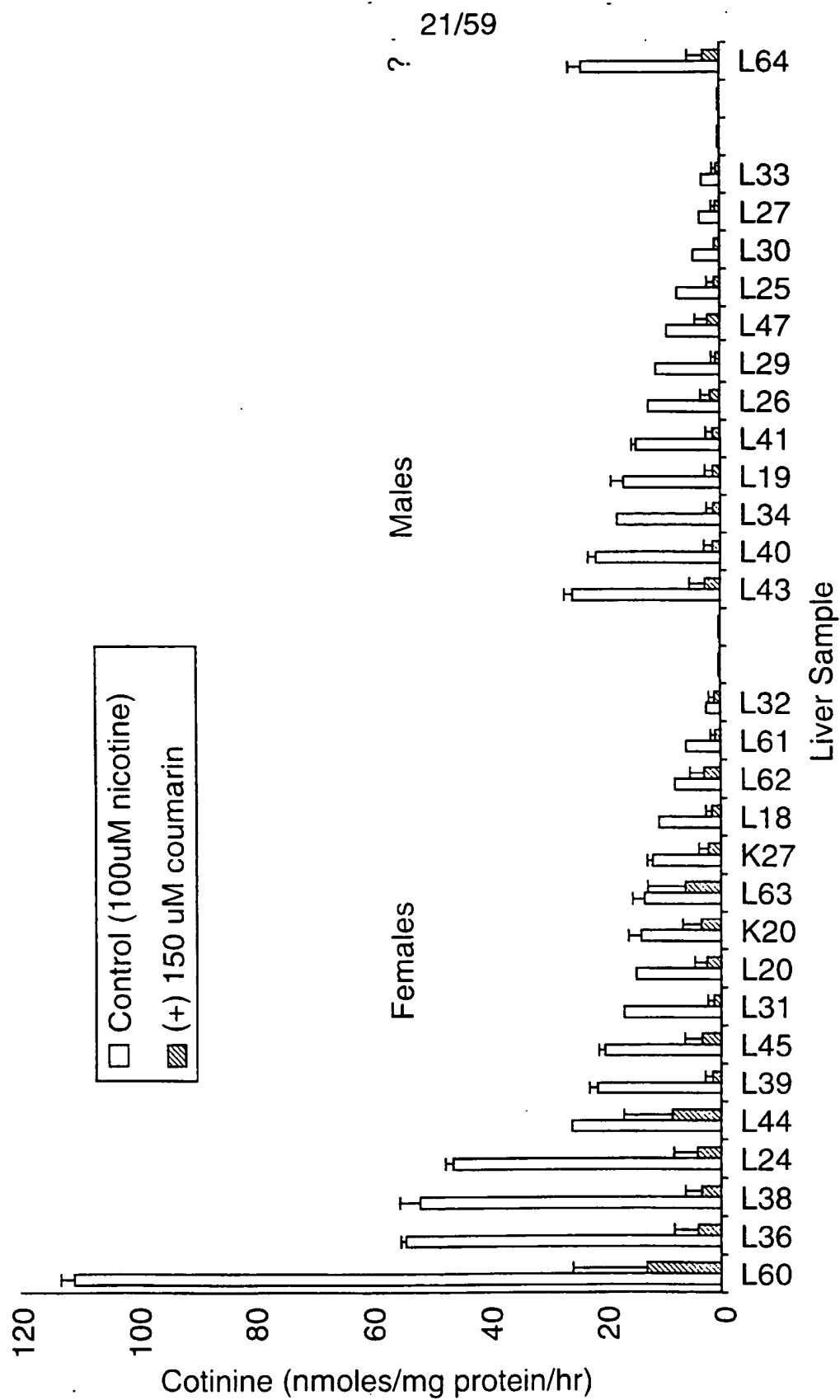
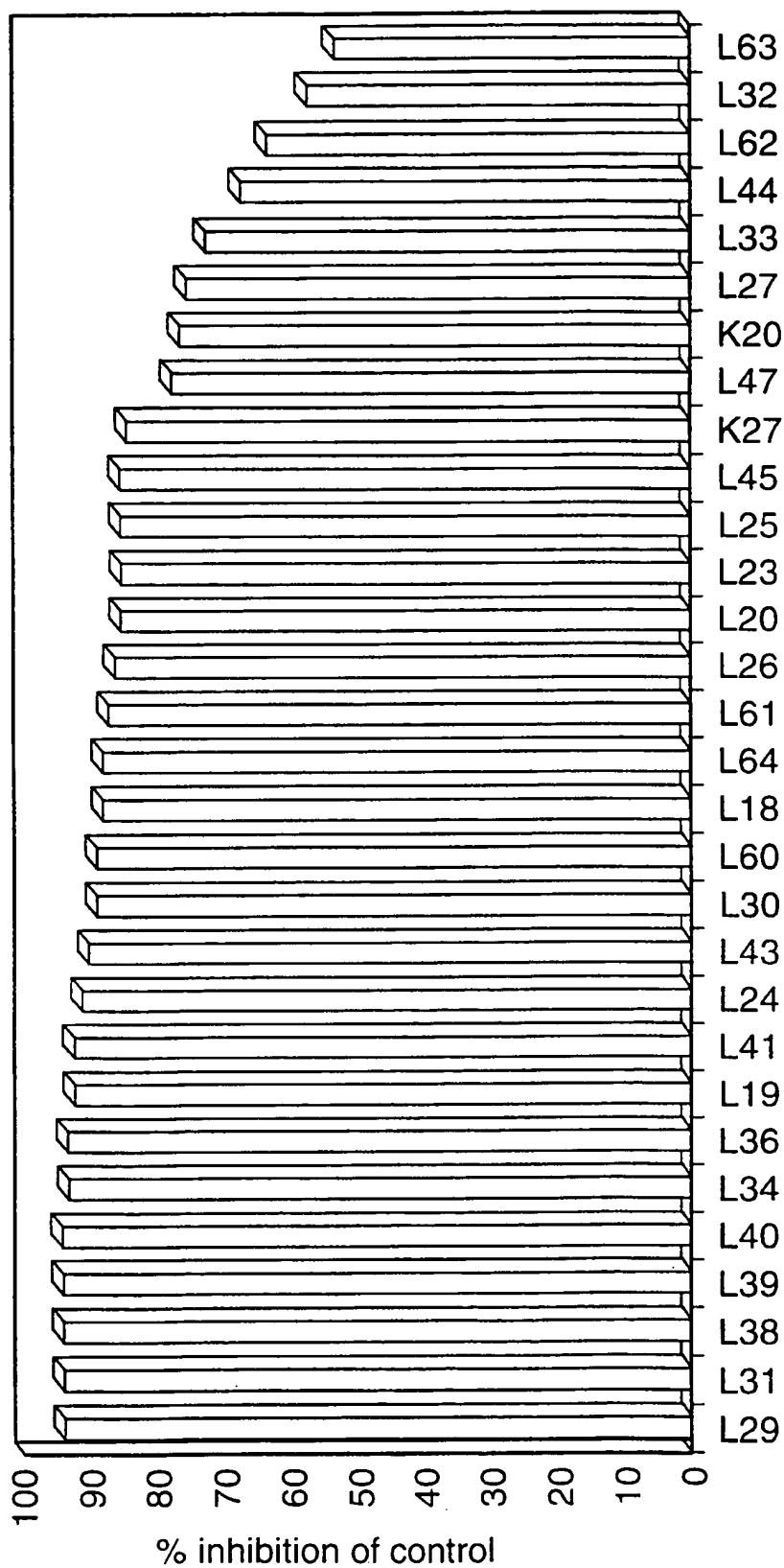


FIG.8B



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Liver Sample

FIG.10

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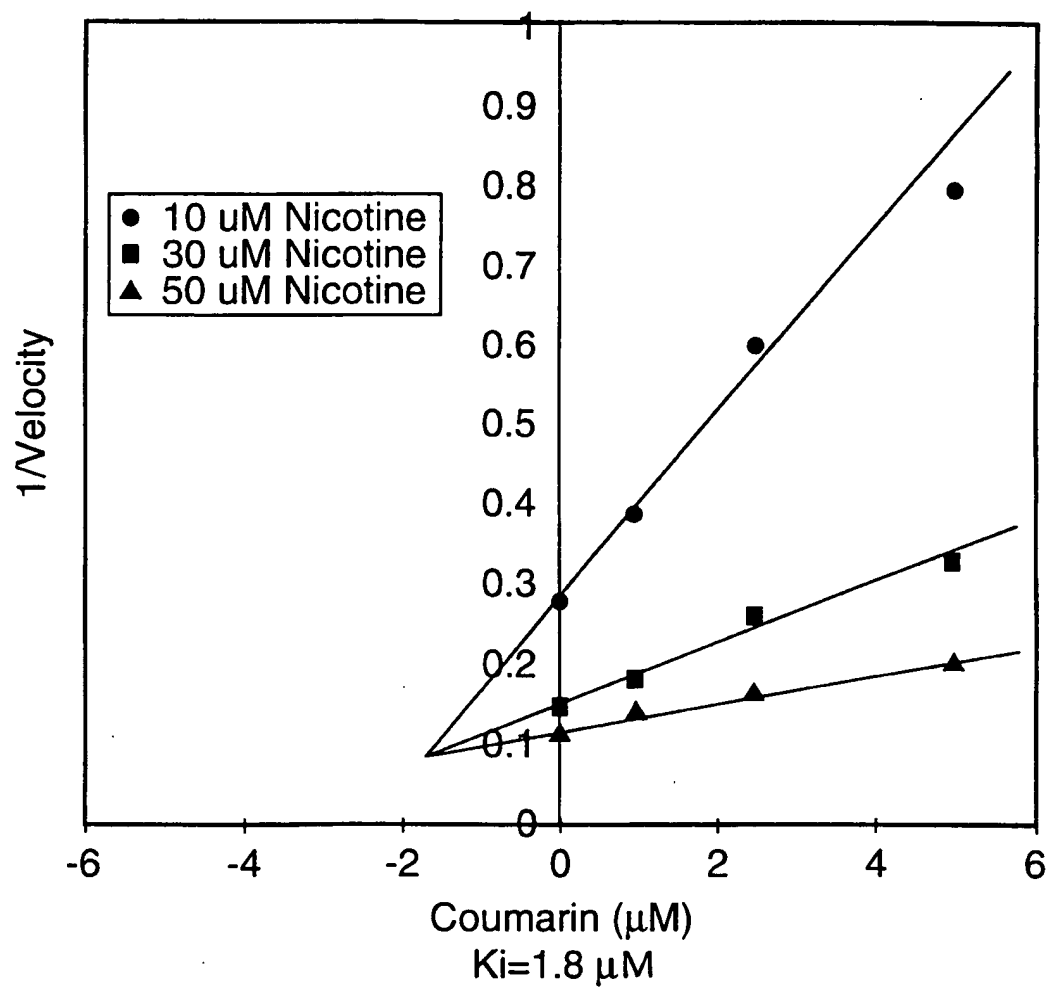
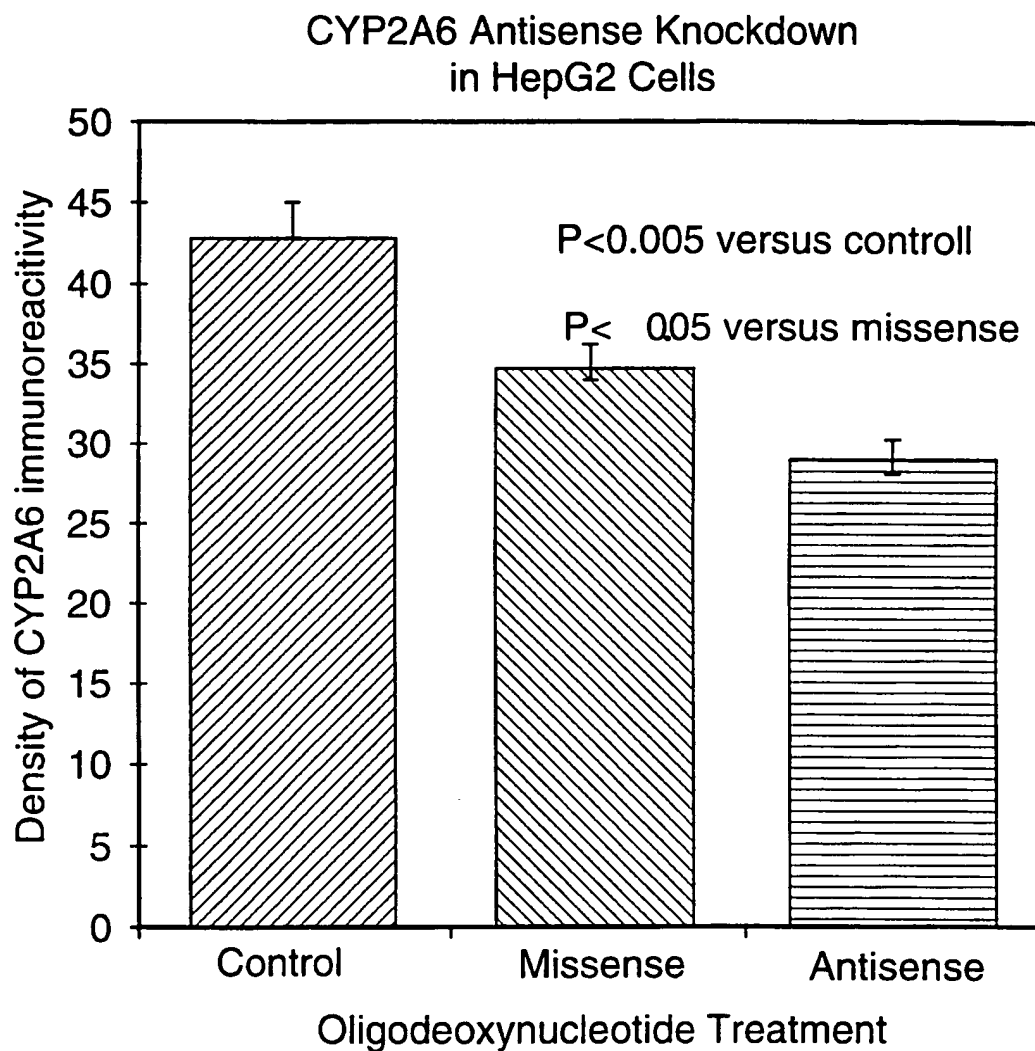


FIG.11

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**FIG.12**

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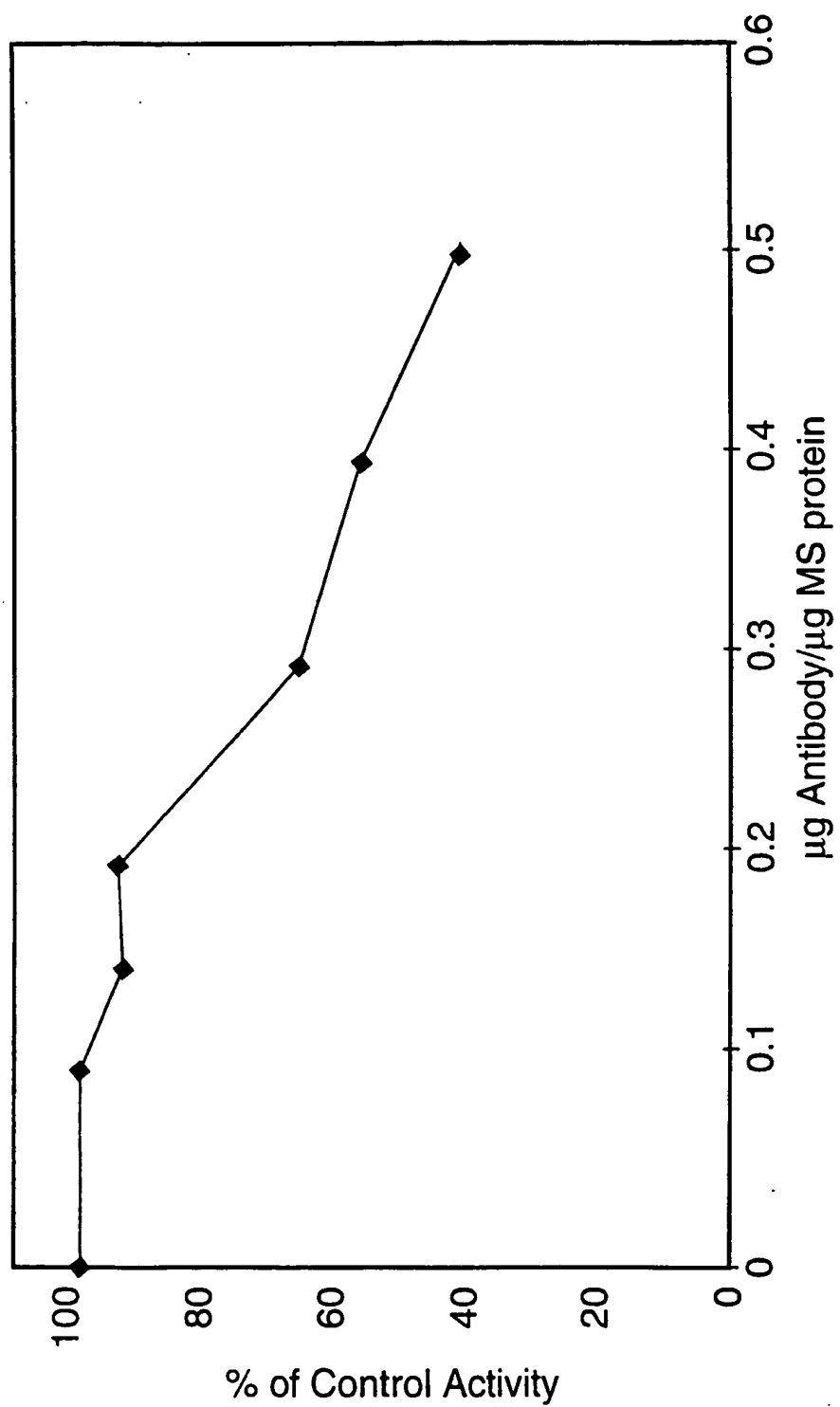
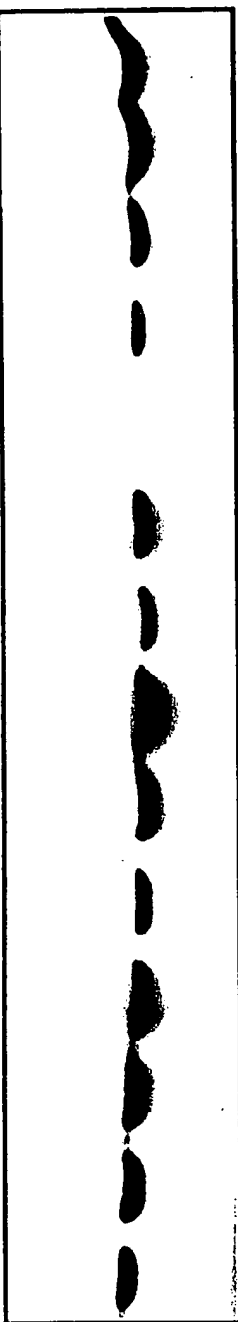


FIG.13

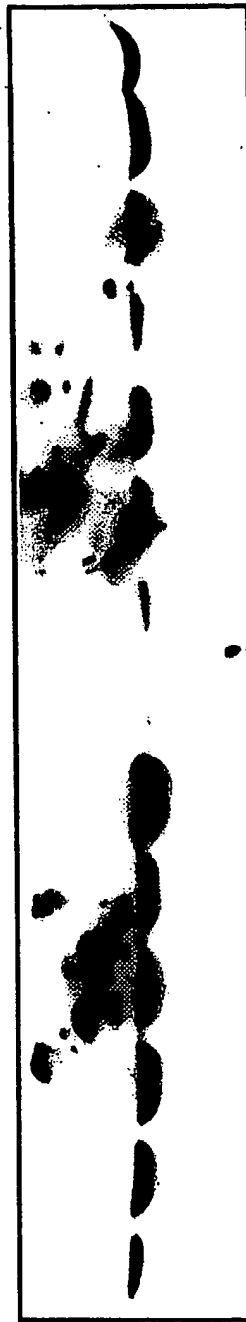
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K20 K27 L18 L19 L20 L23 L24 L25 L26 L27 15 30 75 100



L29 L30 L31 L32 L33 L34 L36 L38 L39 L40 15 30 75 100



L41 L43 L44 L45 L47 L60 L61 L62 L63 L64 15 30 75 100

FIG. 14A.

FIG. 14B.

FIG. 14C.

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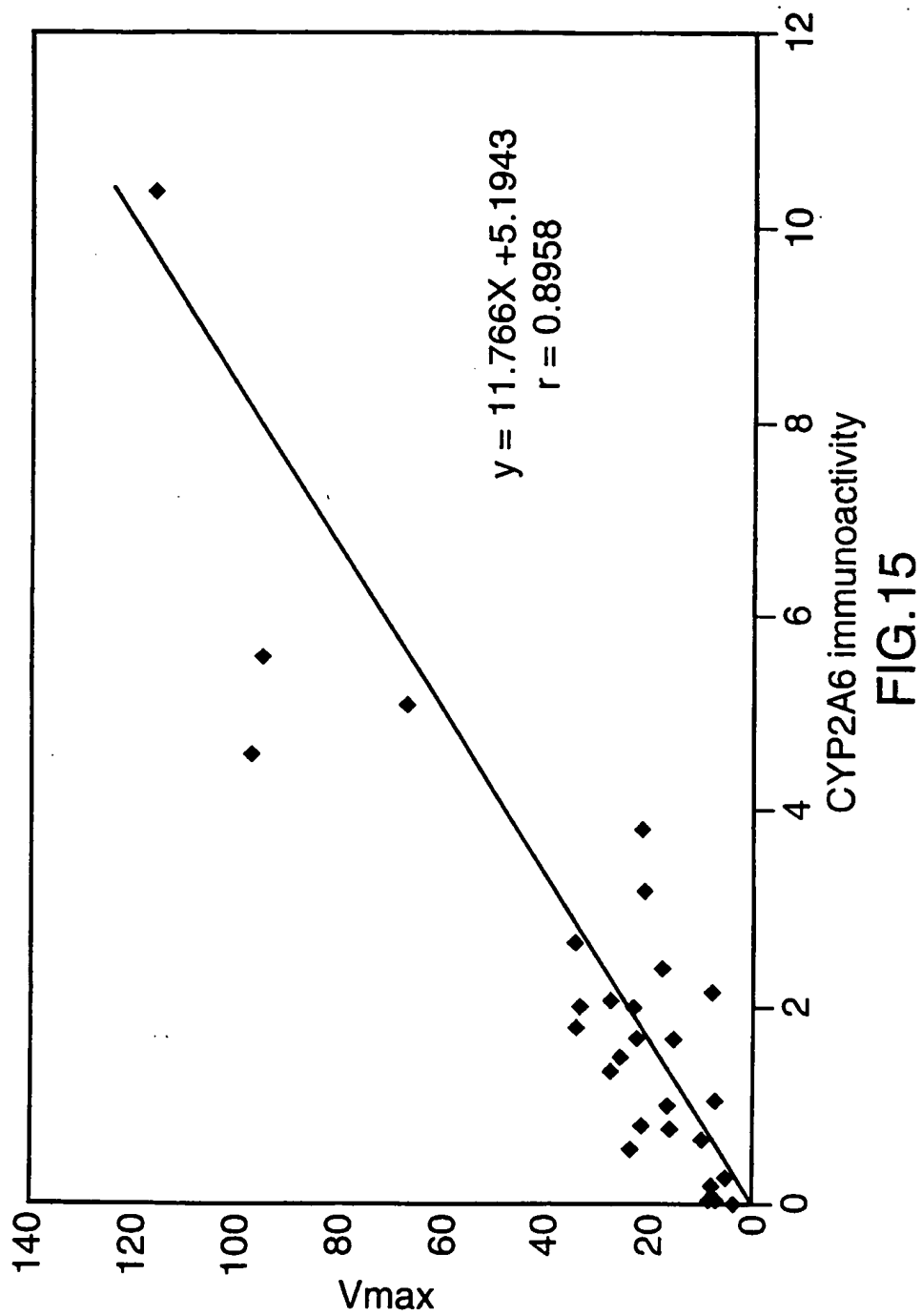
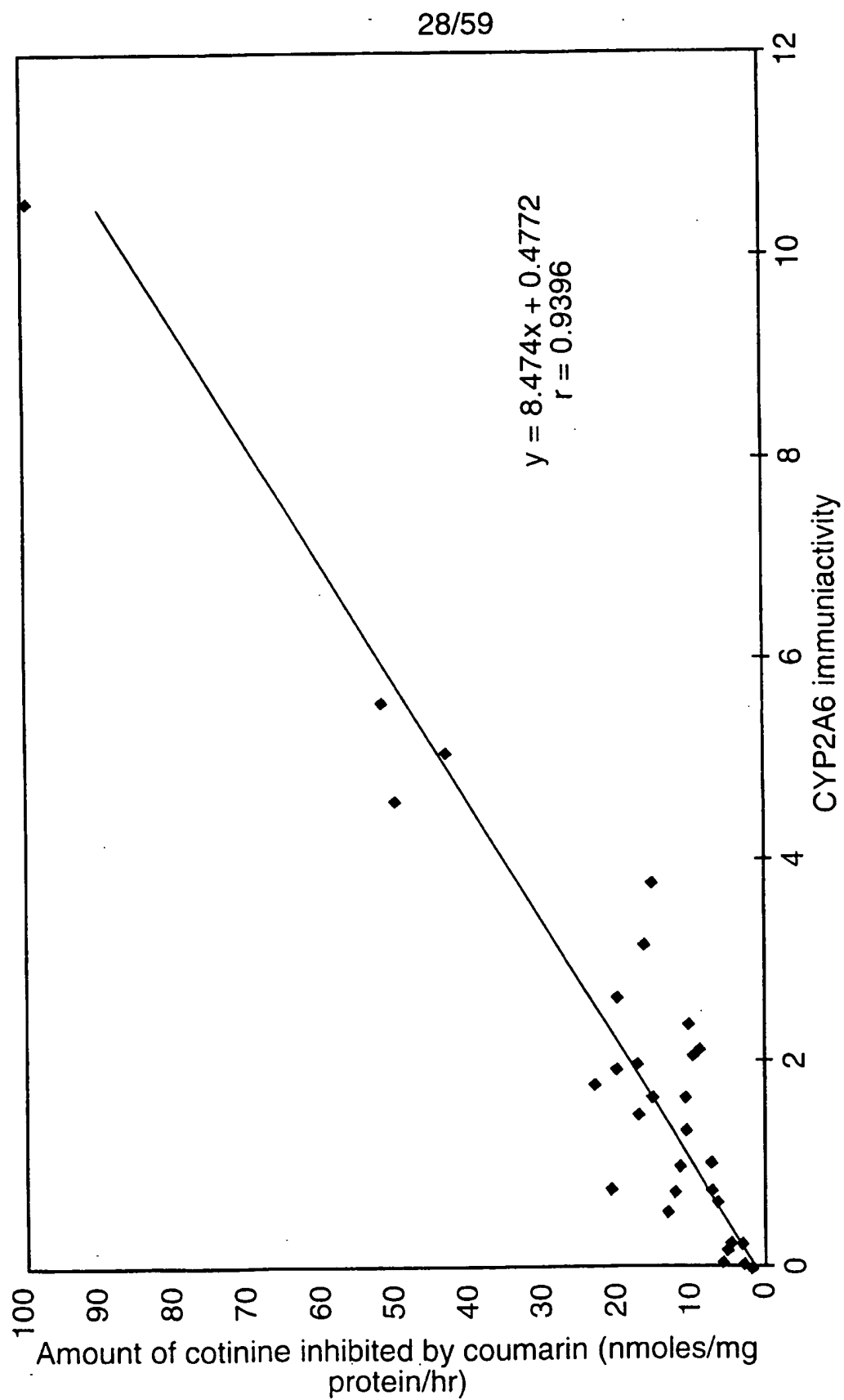


FIG.15



CYP2A6 immunoactivity

FIG.16

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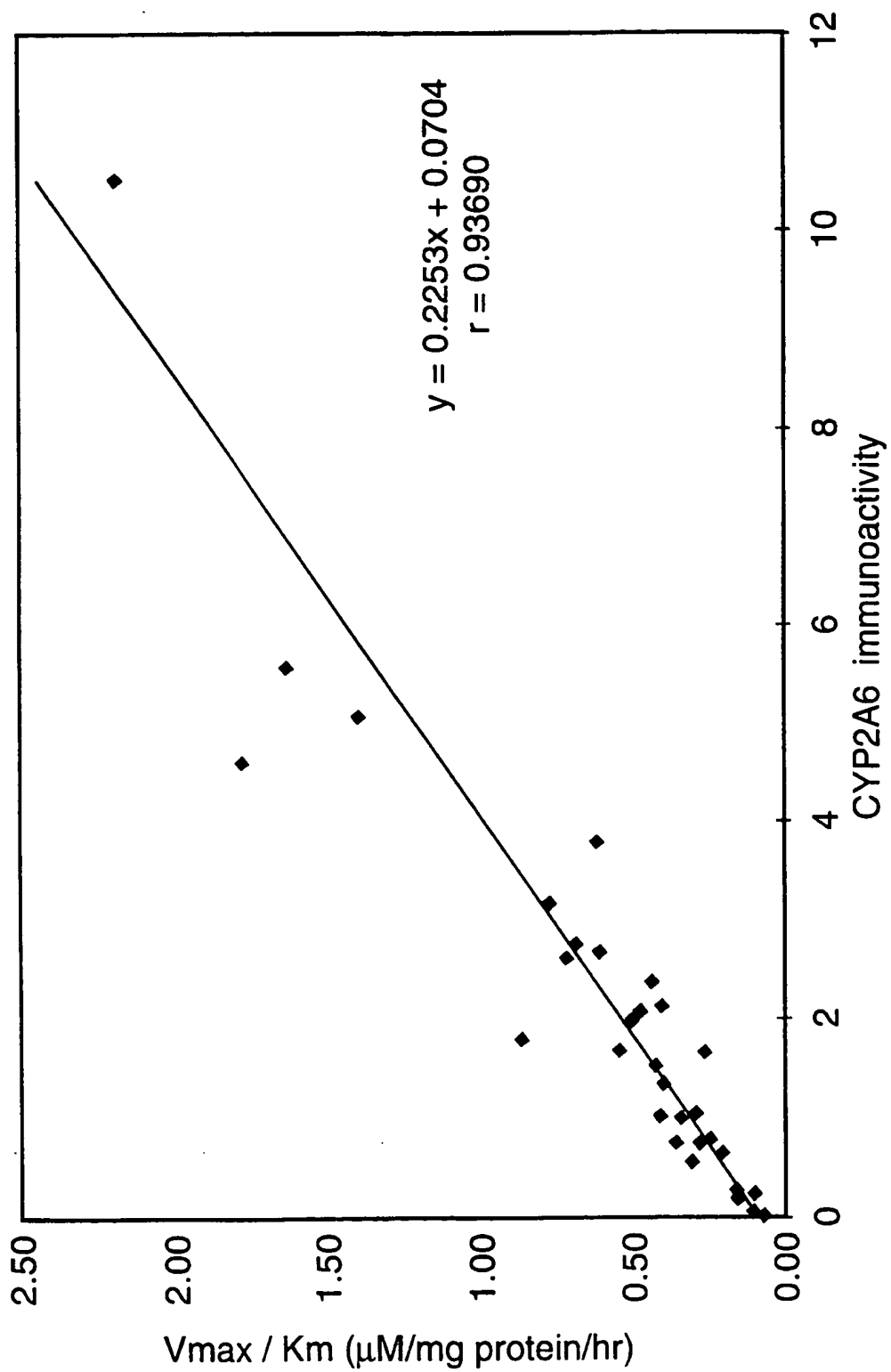
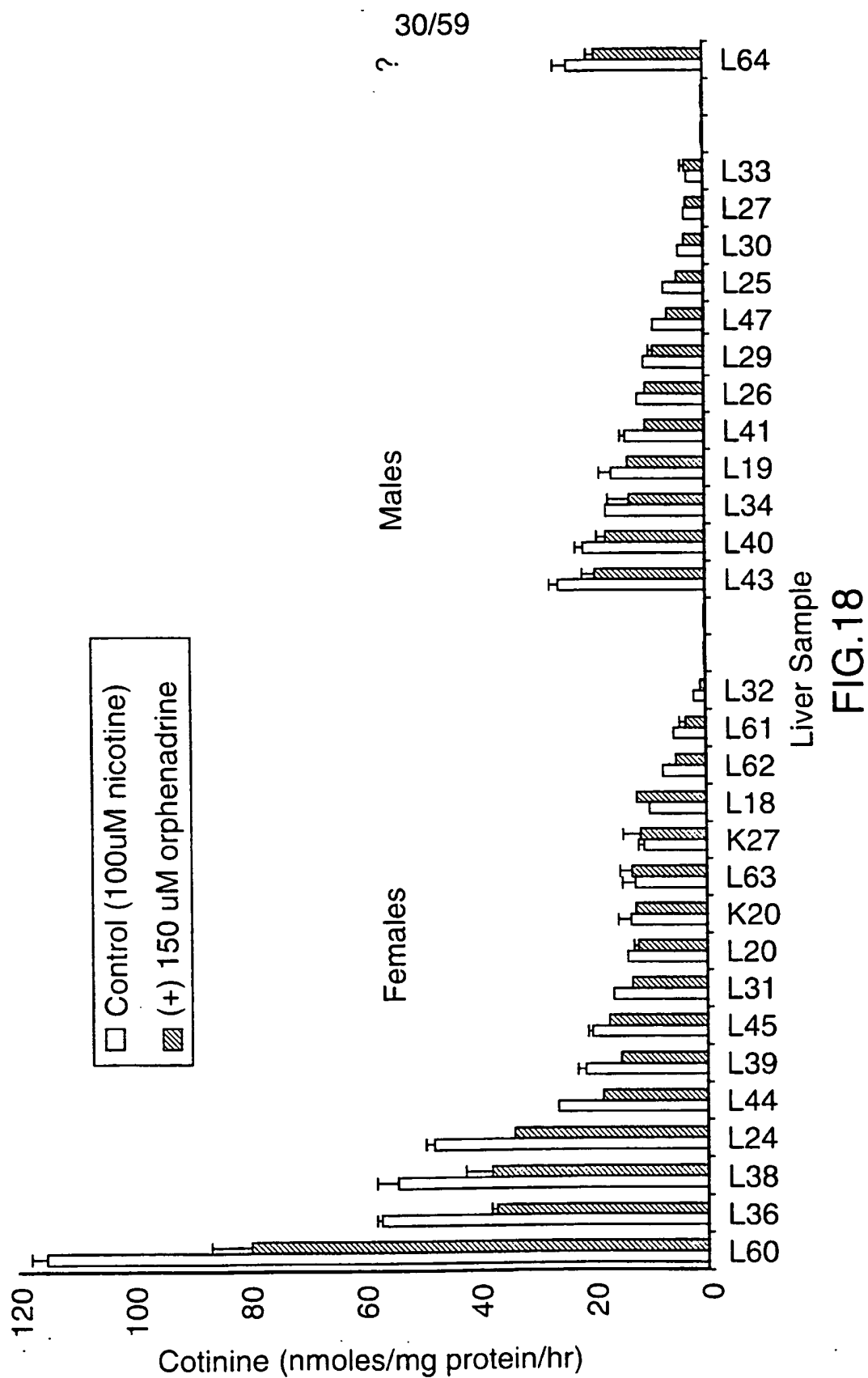
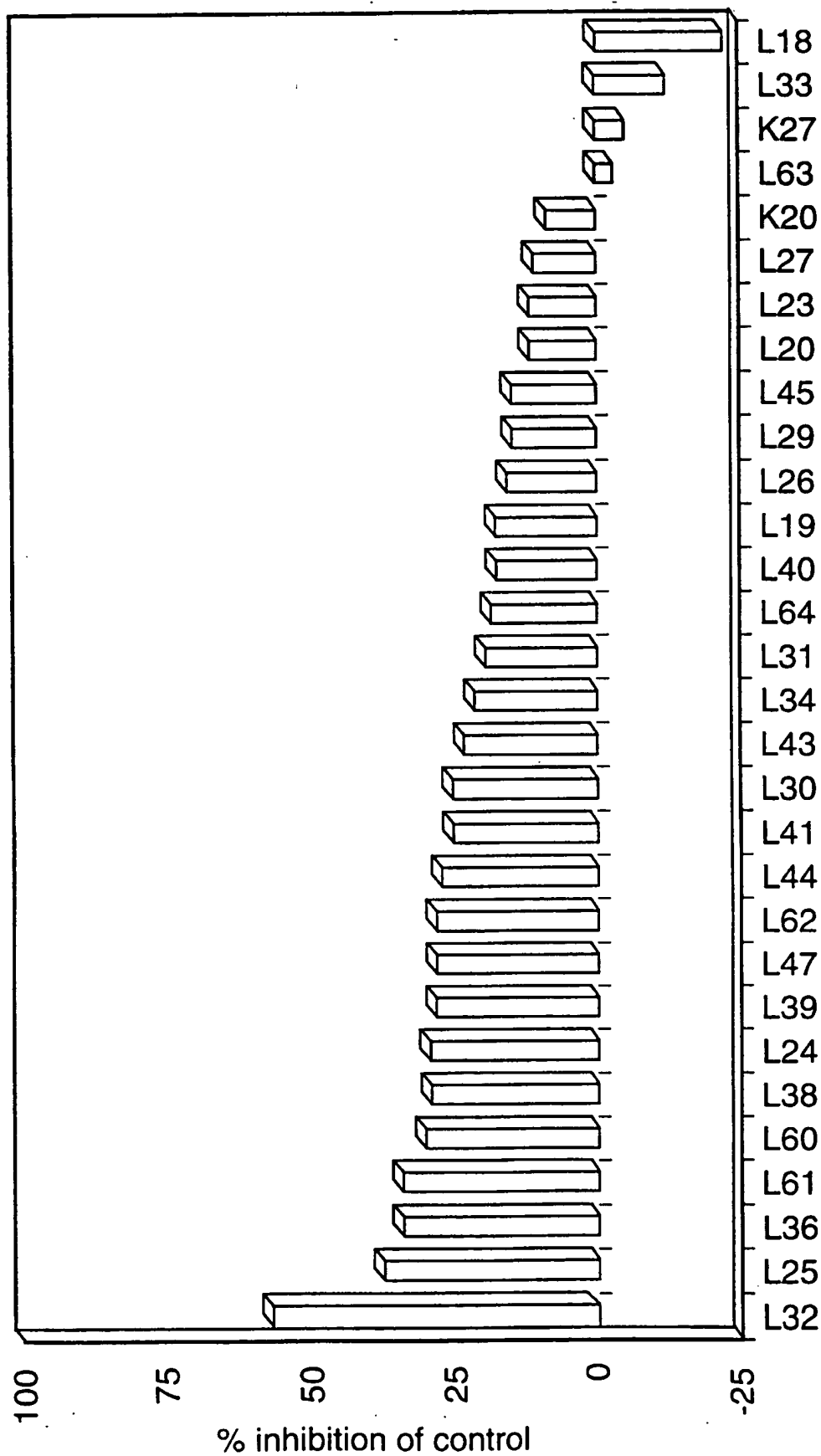


FIG.17



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Liver Sample

FIG.19

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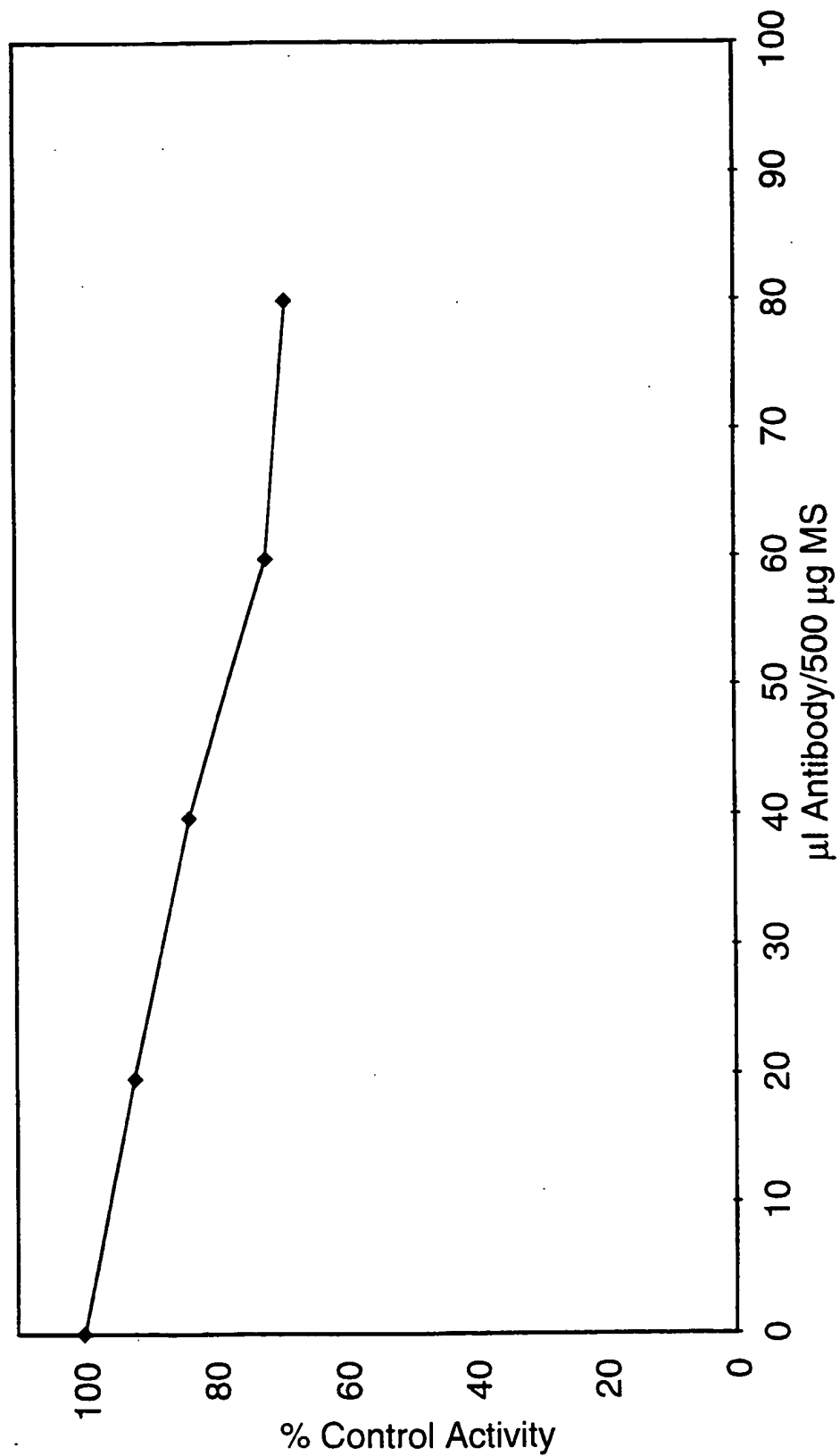


FIG.20

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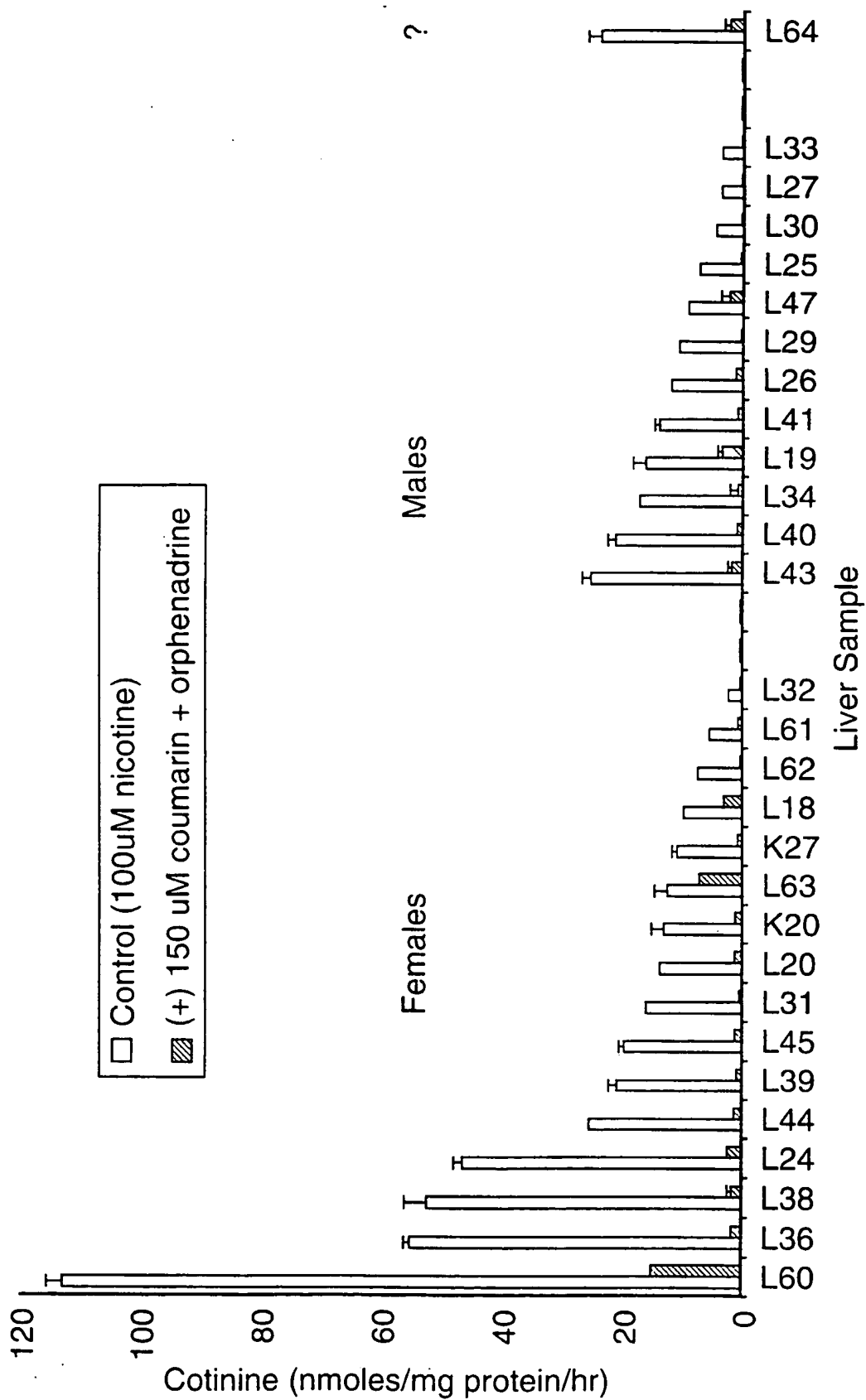
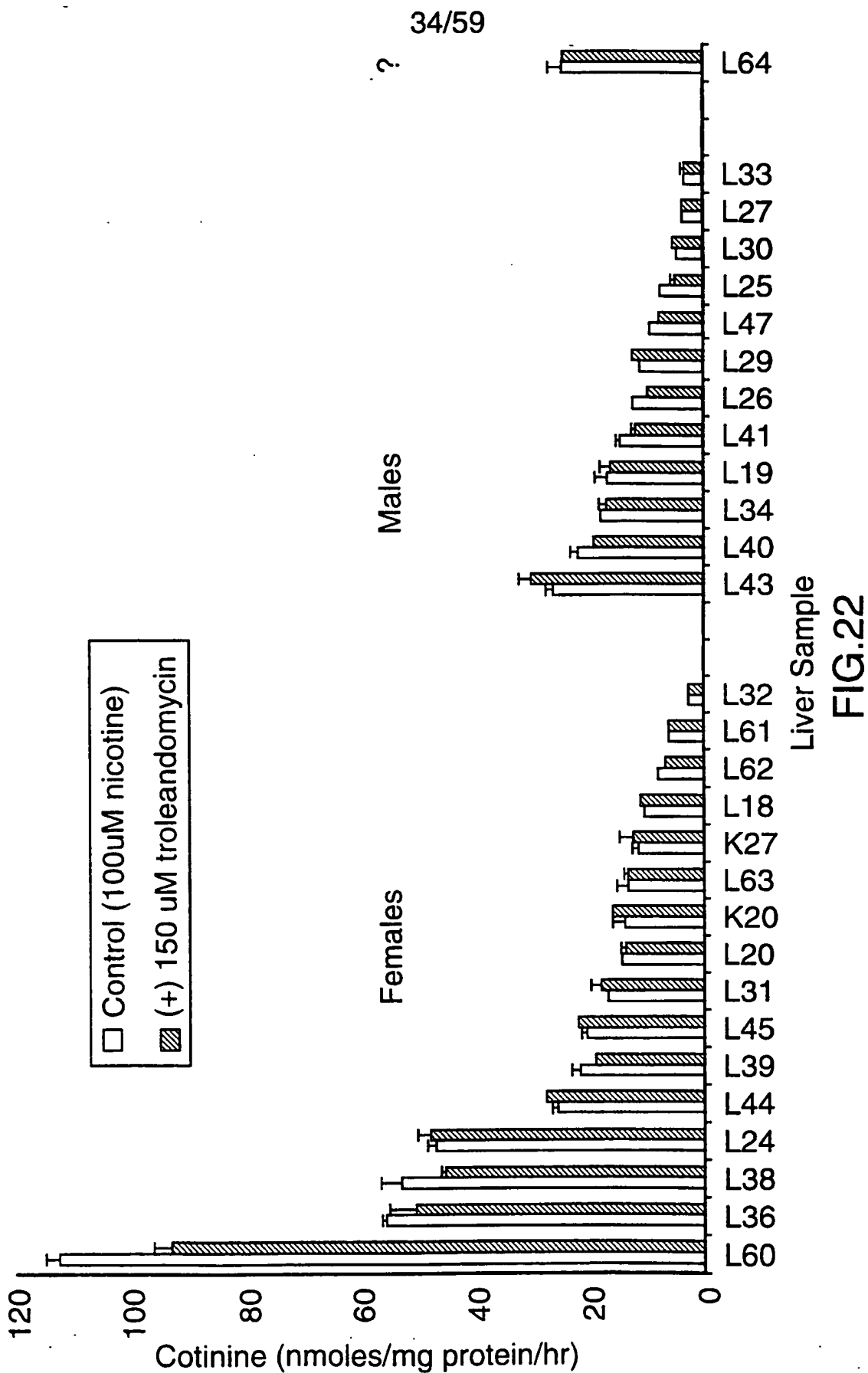


FIG.21



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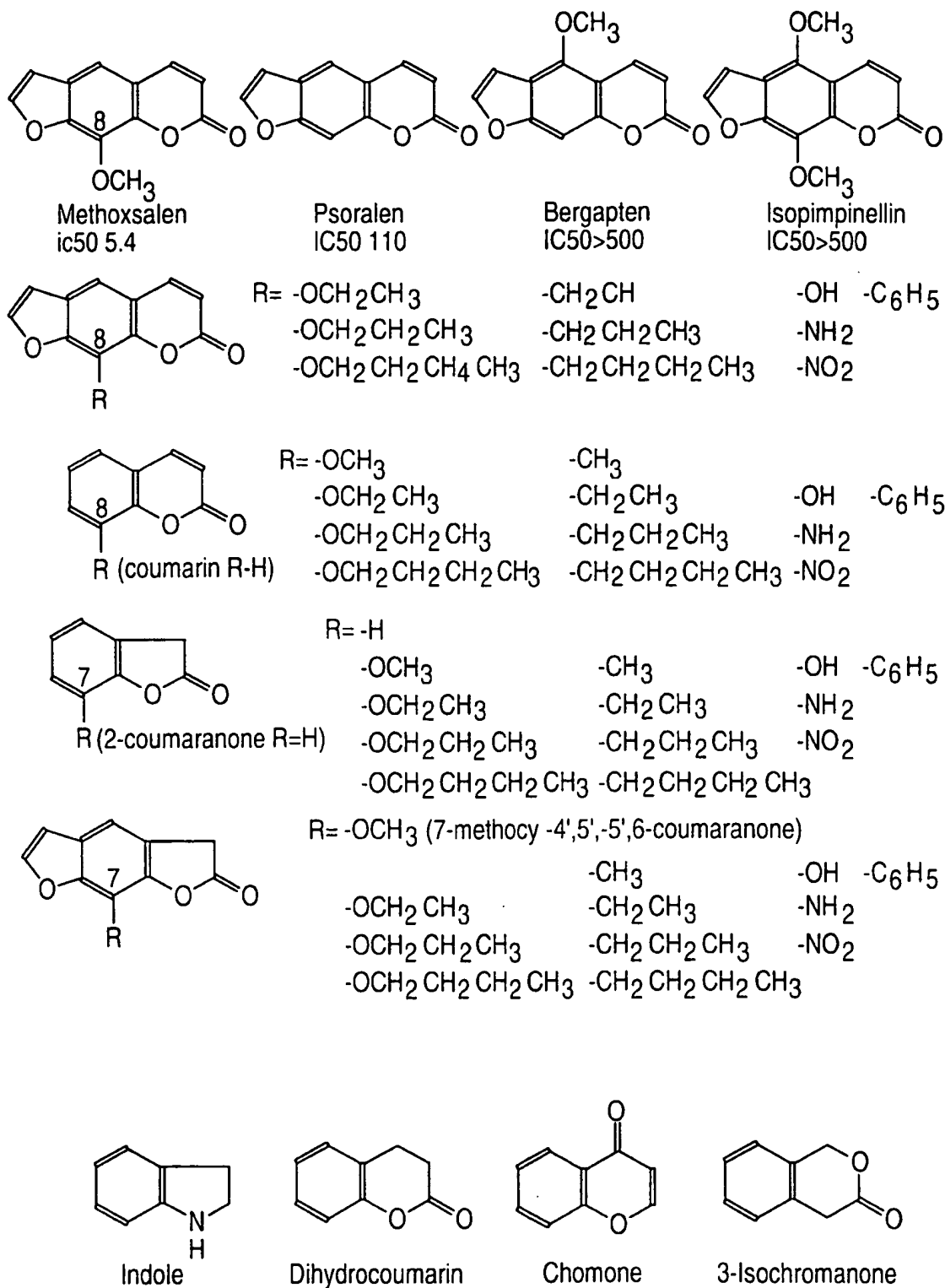
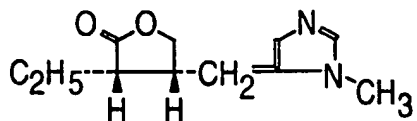
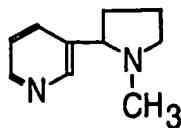


FIG.23A

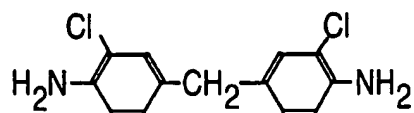
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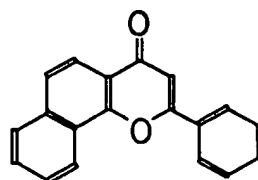
Pilocarpine



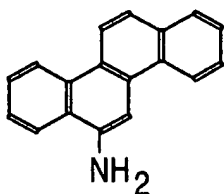
Nicotine



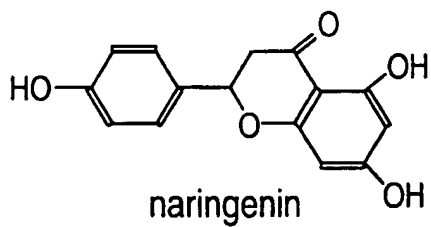
4,4'-Methylene bis[2-chloroaniline]



6-Aminochrysene



α-Naphthoflavone



naringenin

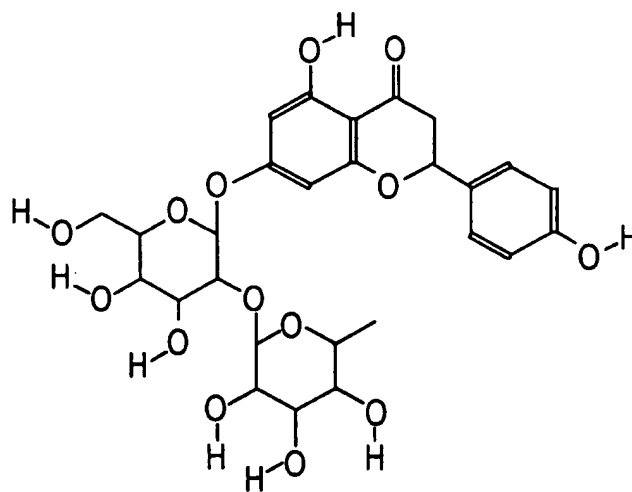
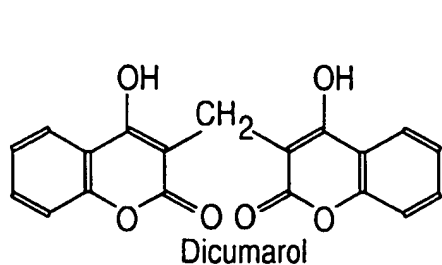
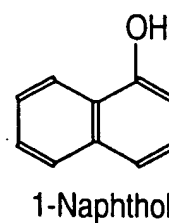
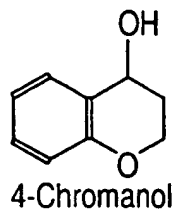
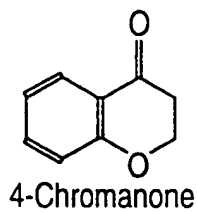
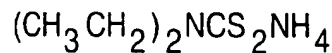
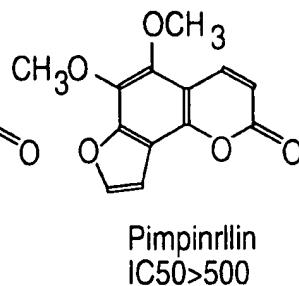
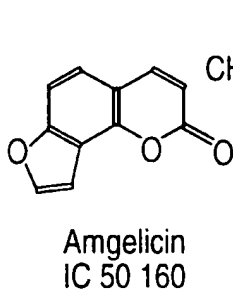
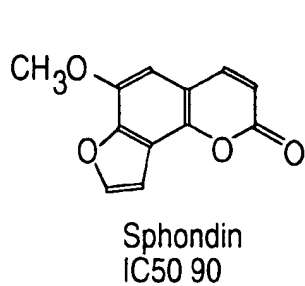
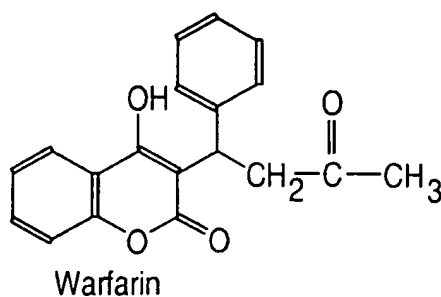
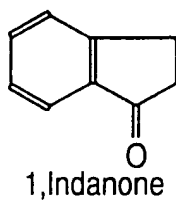
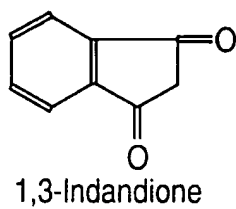
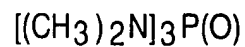
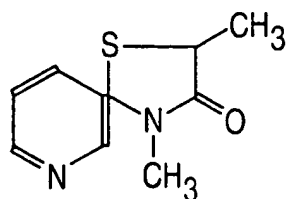


FIG.23B

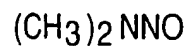
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About 80% activity left at 0.05 mM concentration

70% inhibition at
0.5 mM concentrationDiethyldithiocarbamic acid
ammonium salt

Hexamethylphosphoramidate



N-Nitrosodimethylamine

FIG.23C

FIG.24A

The SAS System
 Experiment BC1; Pharmacokinetics of nicotine
 Revised analysis of kinetics based on re-assays
 Does treatment affect AUC?

----- Compound assayed=COTININE -----

Dependent Variable: AUC

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	10578731978	151124745	4.66	0.0397
Error	6	1944298022	324049670		
Corrected Total	13	12523030000			

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R-Square	0.844742
C.V.	19.80871
Root MSE	18001.38

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SUBJ	6	10548143898	1758023983	5.43	0.0294
TREATMNT	1	30588081	30588081	0.09	0.7690

Least Squares Means

TREATMNT	AUC
	LSMEAN
Methoxsalen10-50	92354.2010
Placebo	89397.9447

FIG.24B

The SAS System
 Experiment BC1; Pharmacokinetics of nicotine
 Revised analysis of kinetics based on re-assays
 Does treatment affect AUC?

----- Compound assayed=NICOTINE -----

Dependent Variable: AUC					
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	54879492.87	7839927.55	5.14	0.0317
Error	6	9143654.02	1523942.34		
Corrected Total	13	64023146.88			
R-Square		C.V.		AUC Mean	
0.857182		17.22829		7165.426	
		Root MSE			
		1234.481			
Source	DF	Type I SS	Mean Square	F Value	Pr > F
SUBJ	6	23085554.55	3847592.43	2.52	0.1422
TREATMNT	1	31793938.32	31793938.32	20.86	0.0038

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Least Squares Means

TREATMNT	AUC
	LSMEAN
Methoxsalen10-50	8672.40779
Placebo	5658.44323

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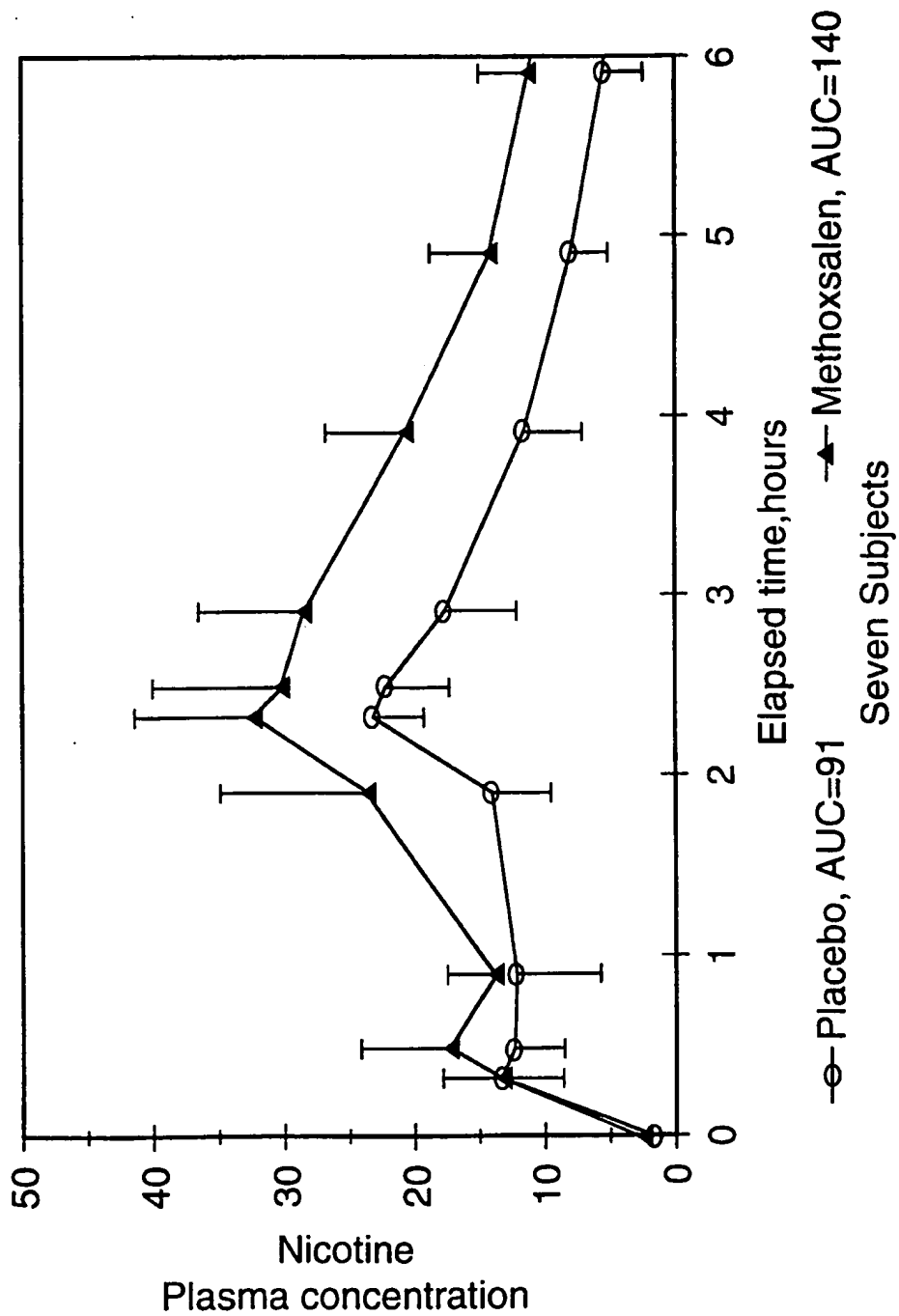


FIG.25

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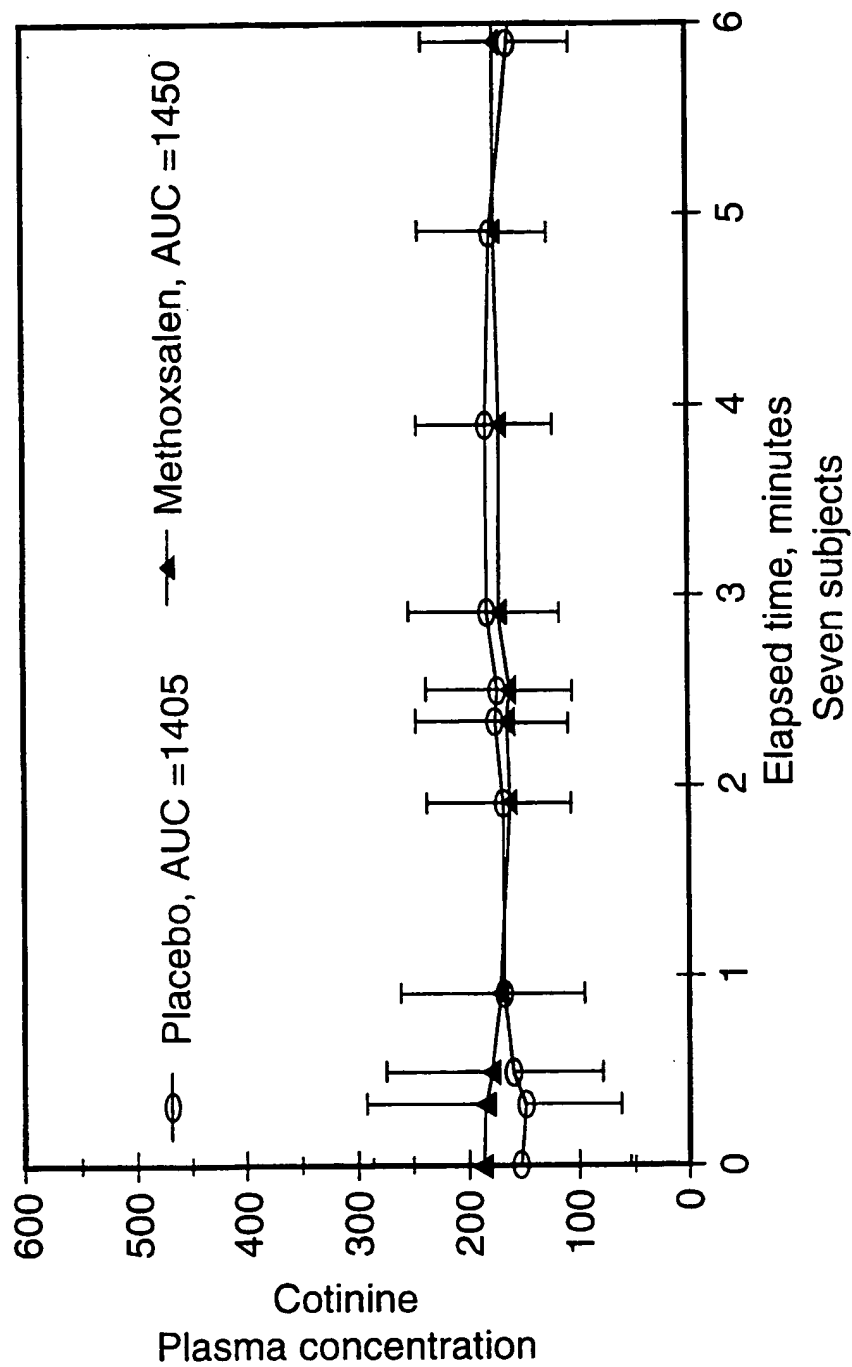


FIG.26

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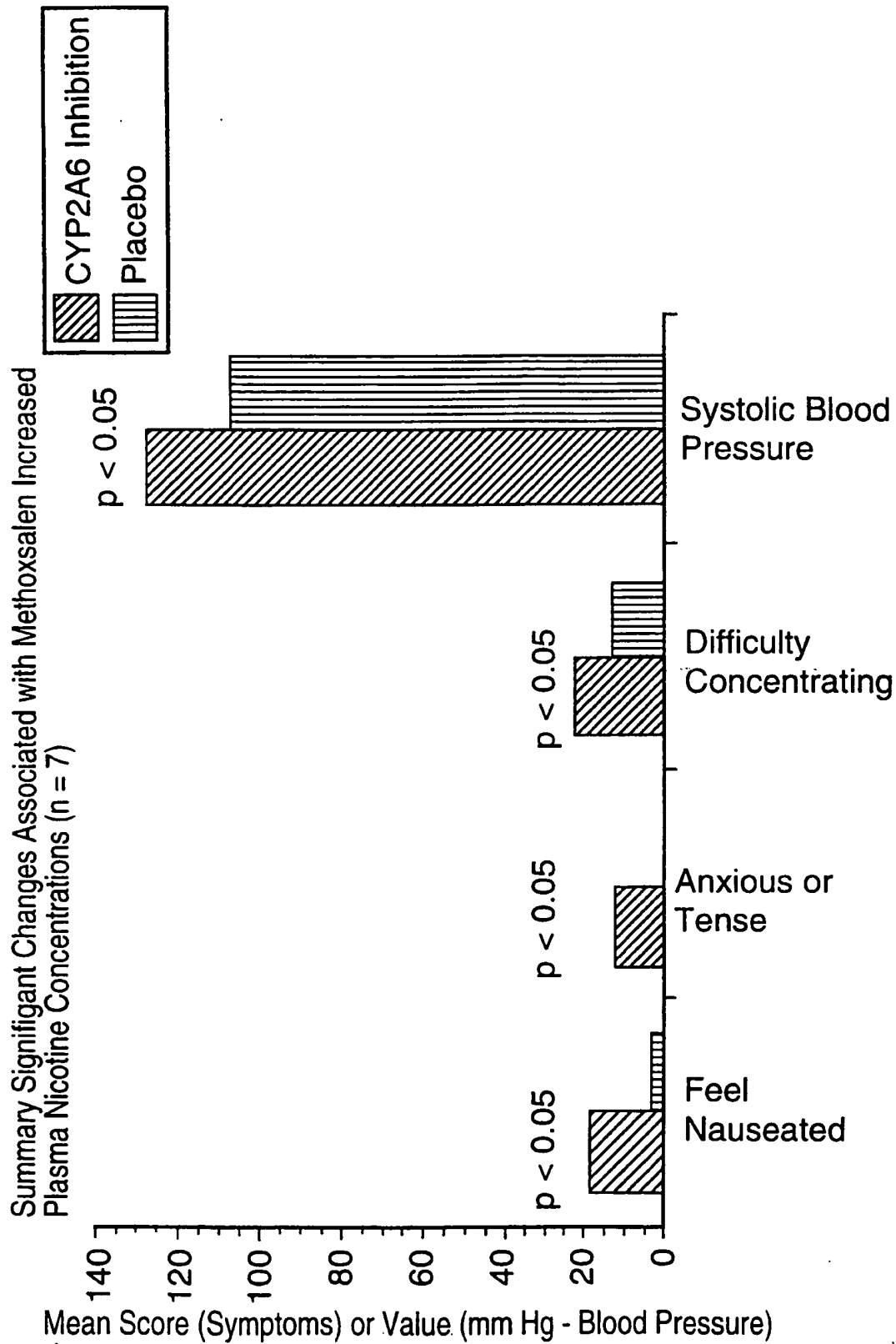
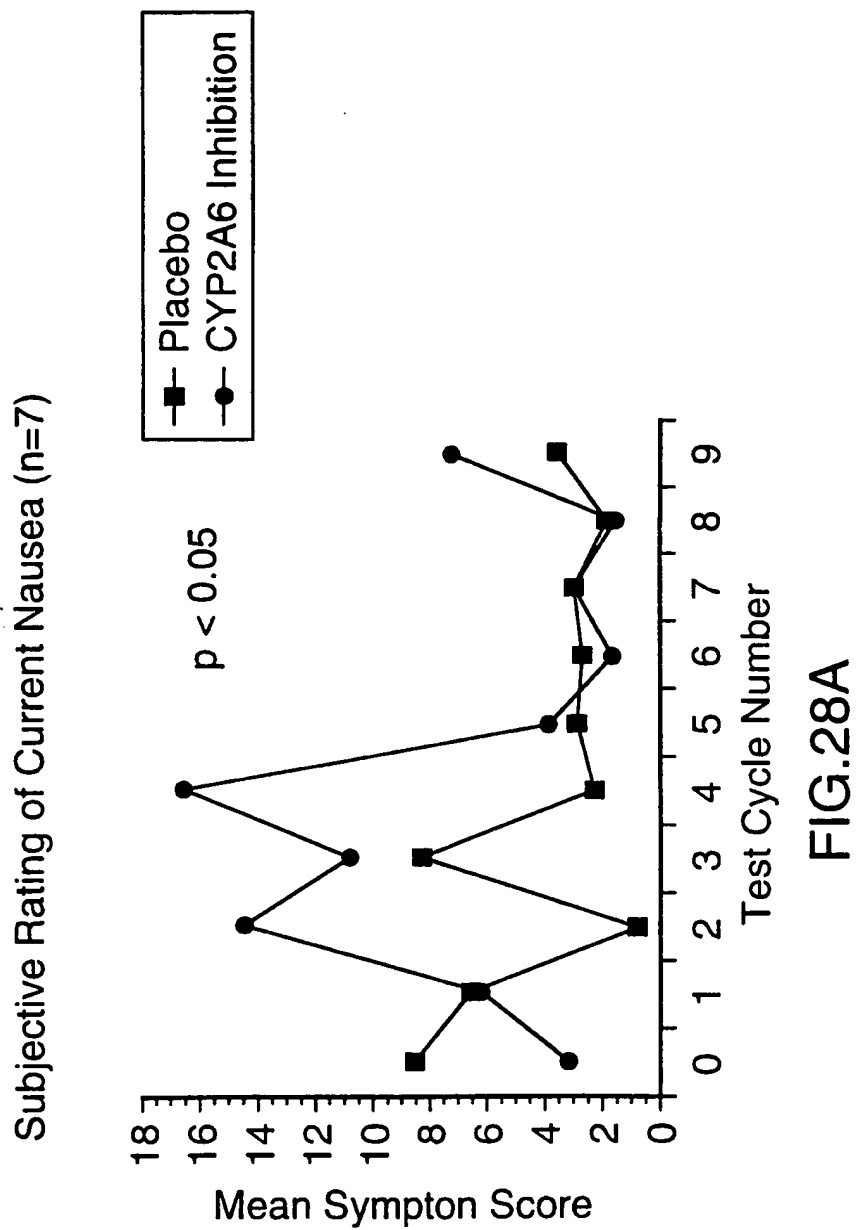


FIG.27

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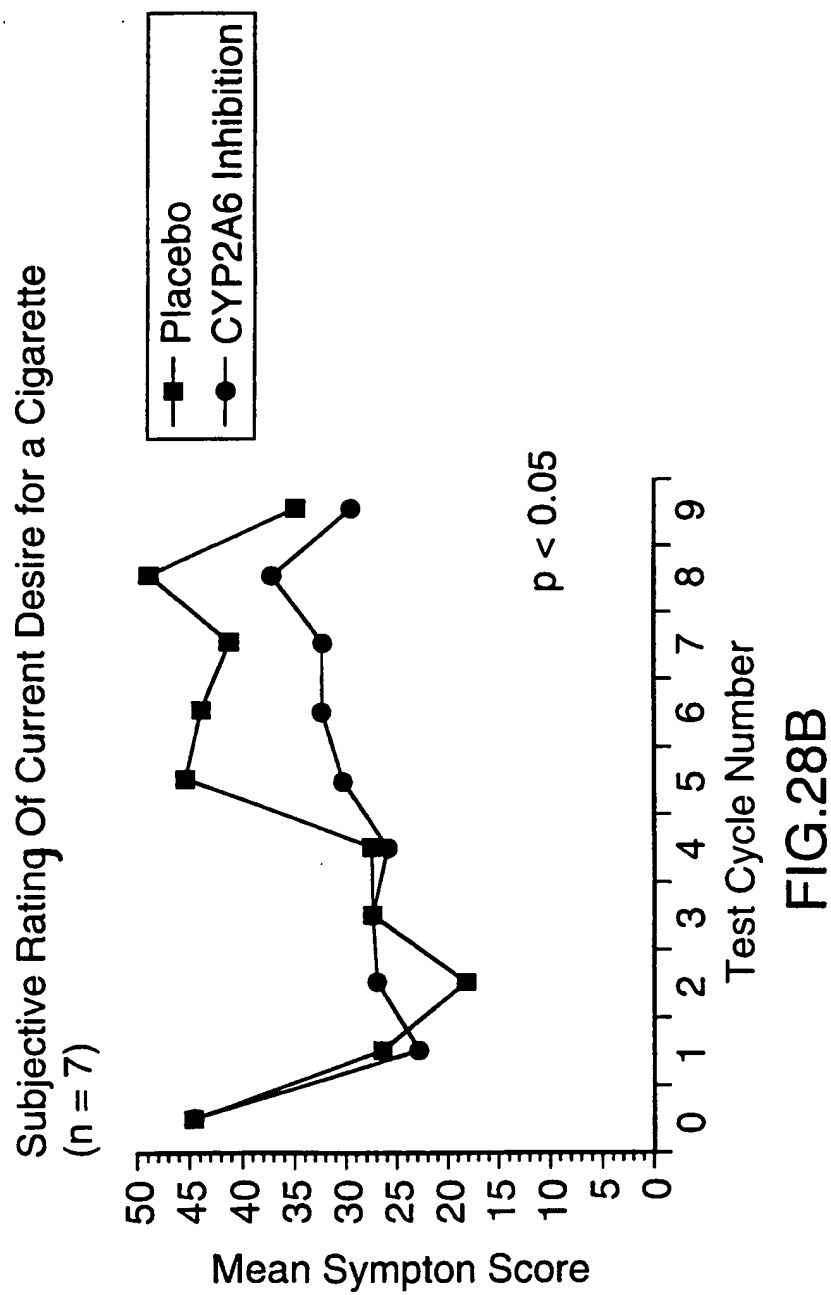


FIG.28B

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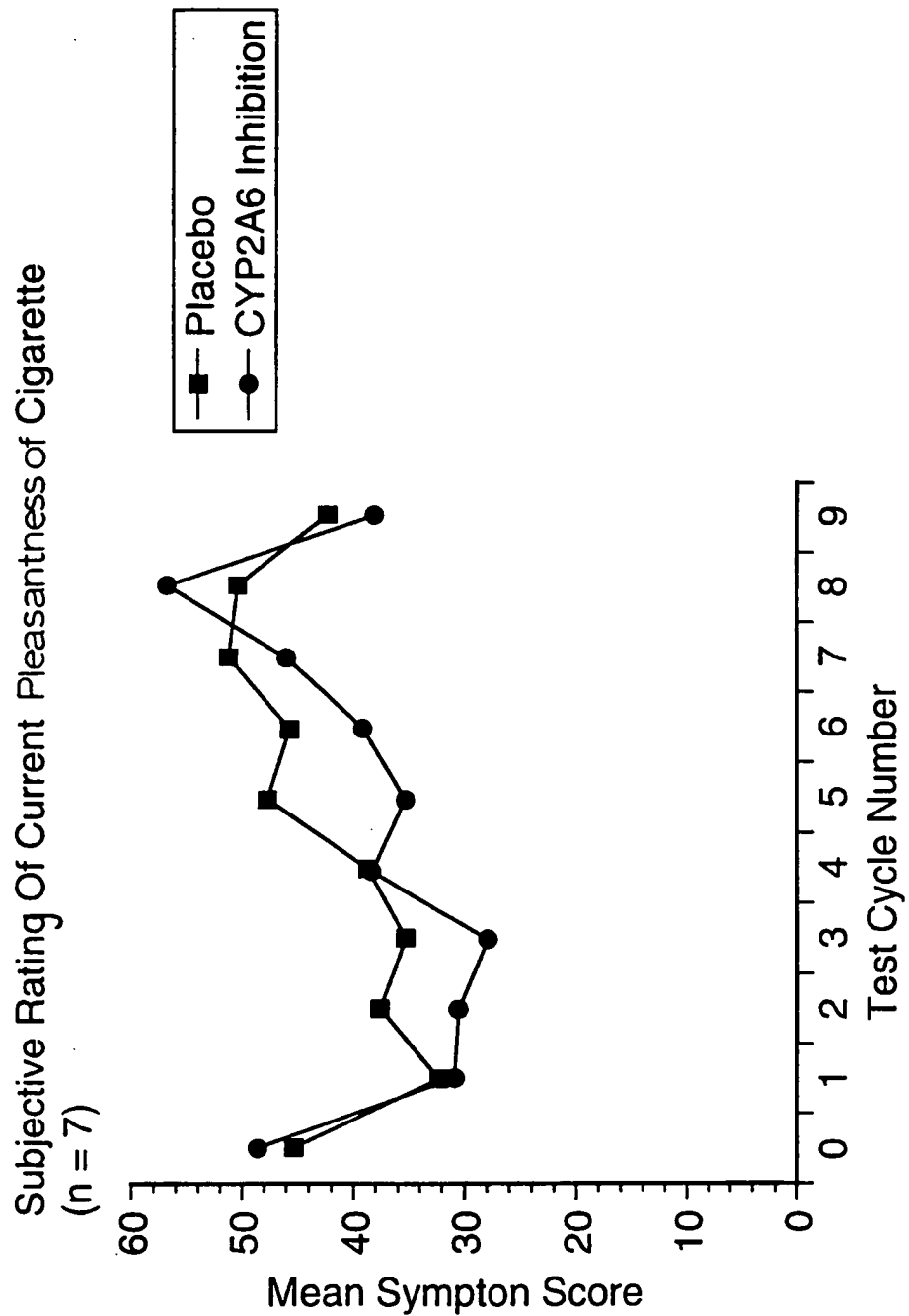


FIG.28C

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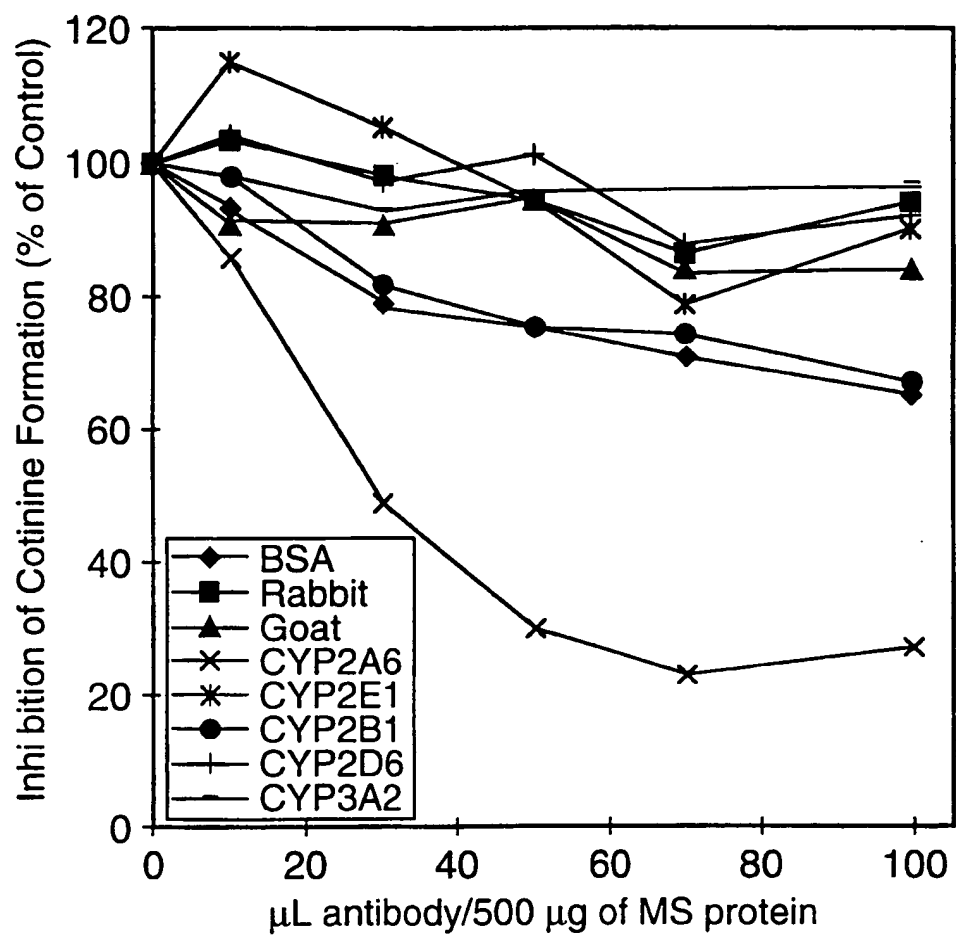


FIG.29

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Inhibition of Nicotine to Cotinine Metabolism by various Compounds

Inhibitor	K _i	% Inhibition at 10 uM	% Inhibition at 100 uM	% Inhibition at 150 uM
coumarin	2 uM (n=4)	65 (n=1)	90 (n=1)	85 +/- 11 (SD, n=31)
7-methoxycoumarin	2.5 uM (n=1)	40 (n=1)	60 (n=3)	—
7-methylcoumarin	15 uM*	20 (n=1)	70 (n=3)	—
7-ethoxycoumarin	>100 uM*	10 (n=1)	20 (n=3)	—
7-hydroxycoumarin	200 uM	—	25 (n=1)	—
diethylthiocarbamic acid	14.5 uM (n=1)	—	—	—
pilocarpine	0.1 uM	—	—	—
naringenin	4.3 uM (n=1)	30 (n=1)	70 (n=3)	—
methoxsalen	0.02 uM (n=1)	—	—	—
naringin	.100 uM*	—	10 (n=1)	—
bupropion	—	20 (n=1)	30 (n=1)	—
orphenadrine	—	—	—	20 +/- 16 (SD, n=30)
troleandomycin	—	—	—	3 +/- 11 (SD, n=30)

all nicotine concentrations were at the K_m value for cotinine formation in their respective livers
** estimated from screening studies with 10 and 100 uM inhibitor concentrations*

FIG.30A

Ki Values for the Inhibition of the CYP2A6 Substrate Coumarin to 7-Hydroxycoumarin Metabolism by various compound

Inhibitor	Human liver	Monkey liver
methoxsalen	0.29 uM	1.69 uM
nicotine	100.1 uM	24.1 uM
pilocarpine	0.9 uM	0.9 uM

FIG.30B

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Effect of Various Compounds on Cotinine Formation

% control cotinine formation

Inhibitor	10 μ M	100 μ M
coumarin	35	10
naringenin	70	30
7-methylcoumarin	80	30
7-methoxycoumarin	60	40
bupropion	80	70
7-ethoxycoumarin	90	80

FIG.30C

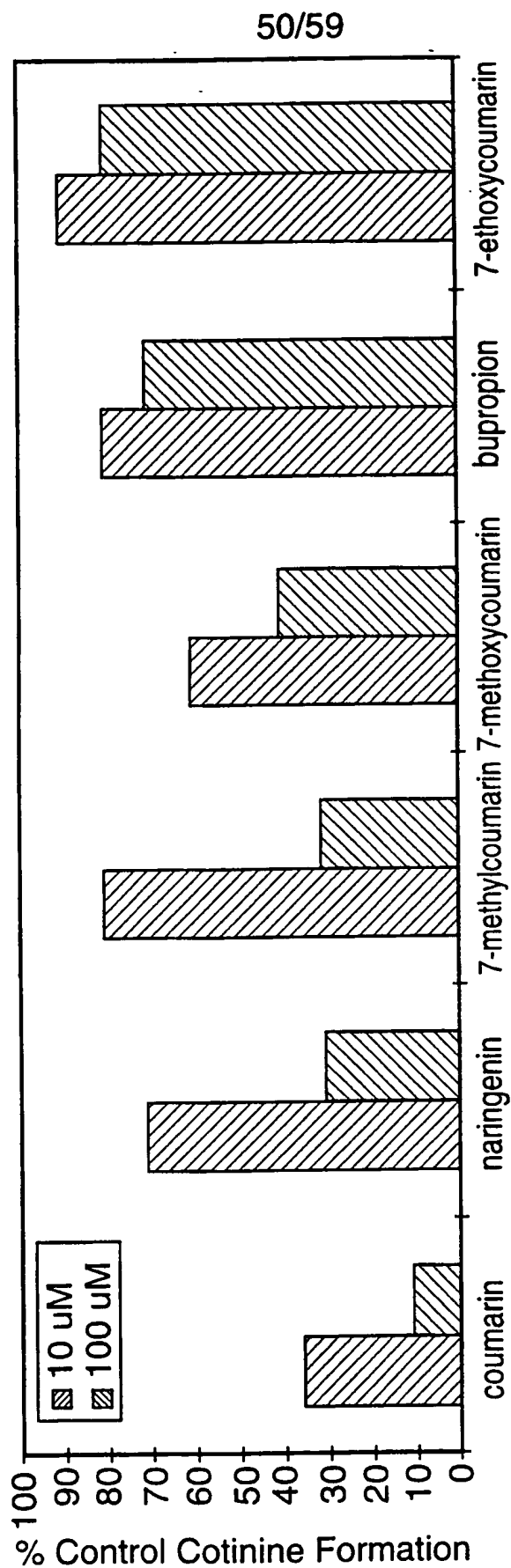


FIG.30D

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Dixon Plot of 7-Methoxycoumarin Inhibition of Nicotine to Cotinine Formation in K28 Human Liver Microsomes

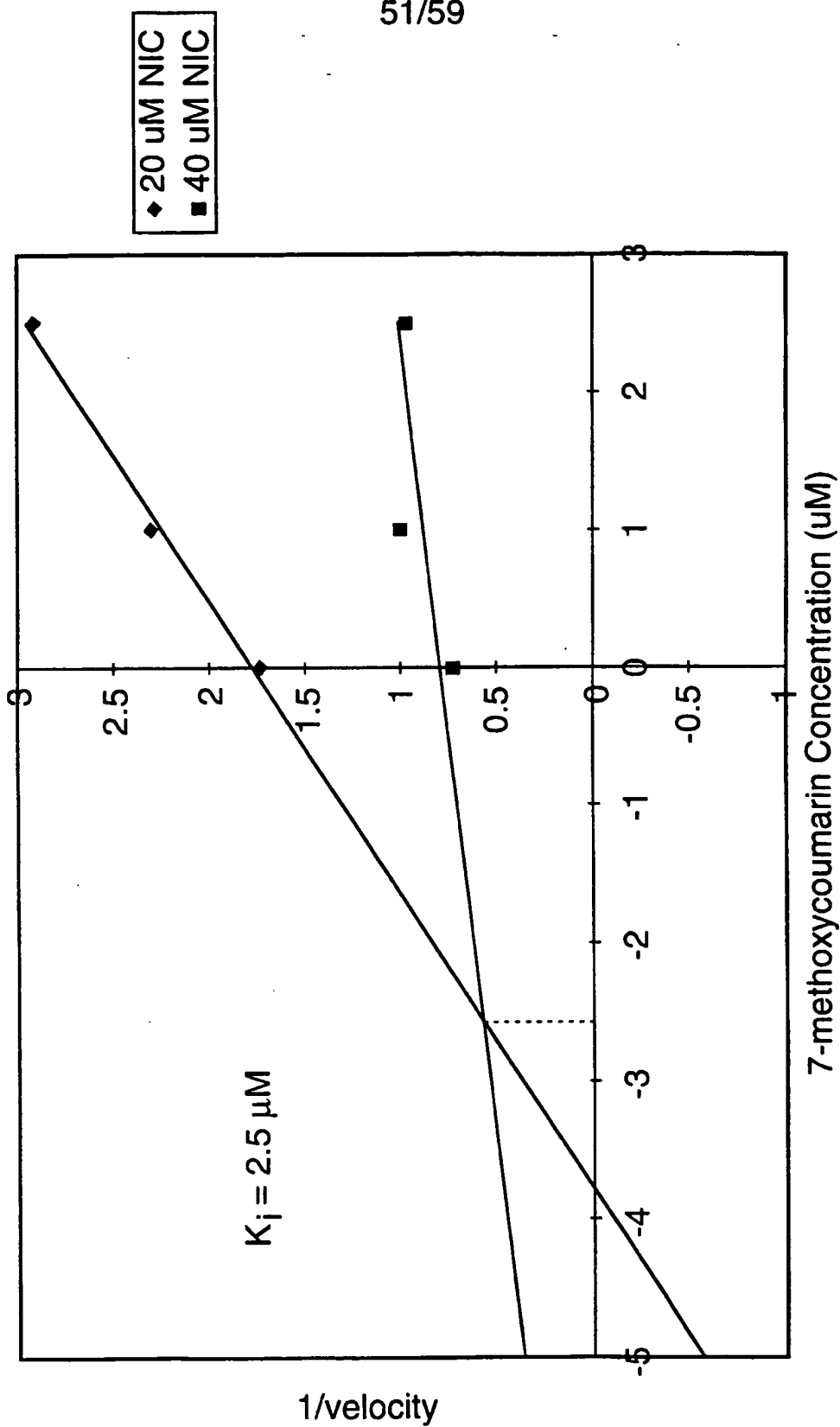


FIG.31

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Dixon Plot of Methoxsalen Inhibition of Nicotine to Cotinine Formation with 10 Minute
Preincubation in K28 Human Liver Microsomes

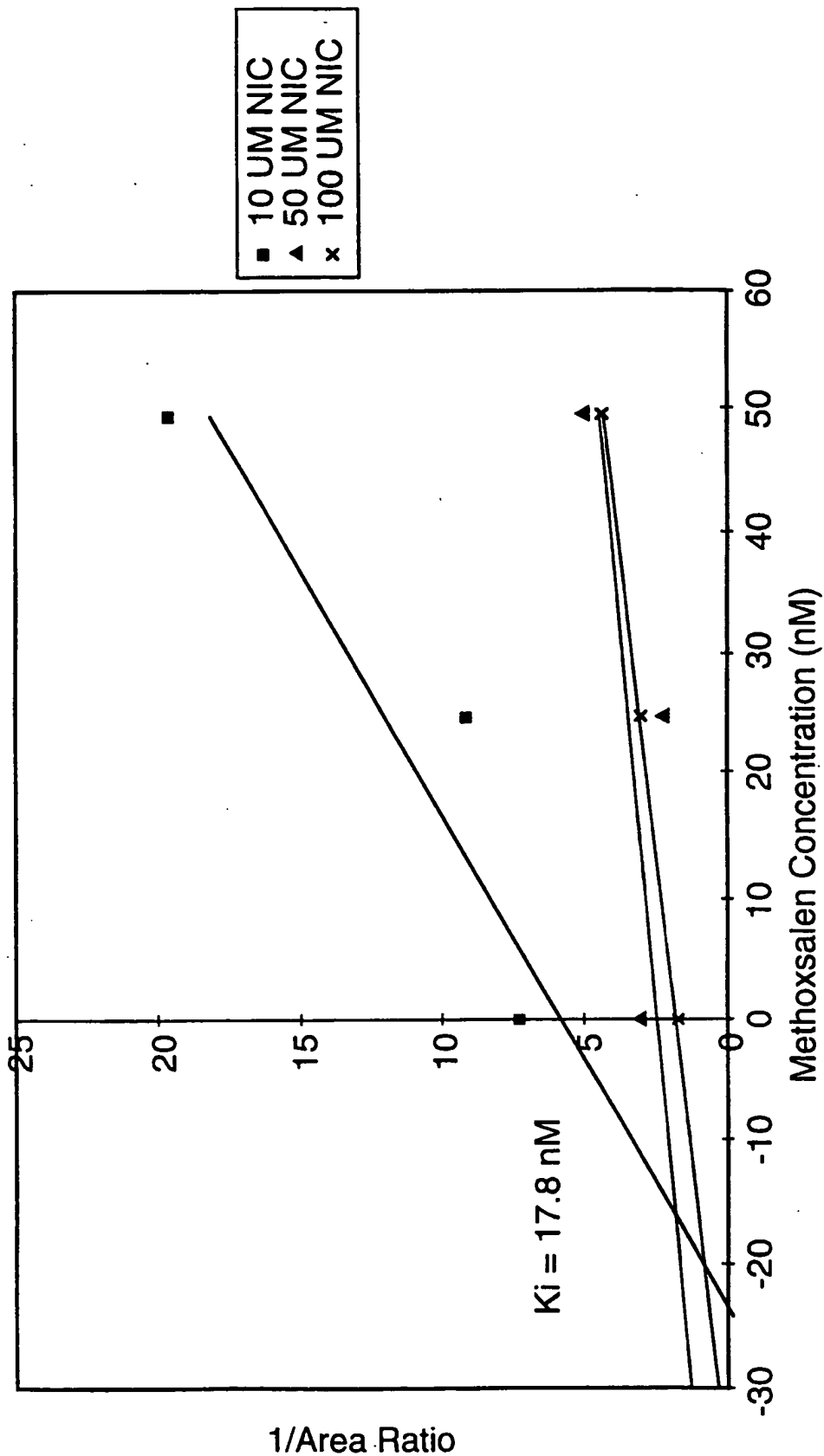
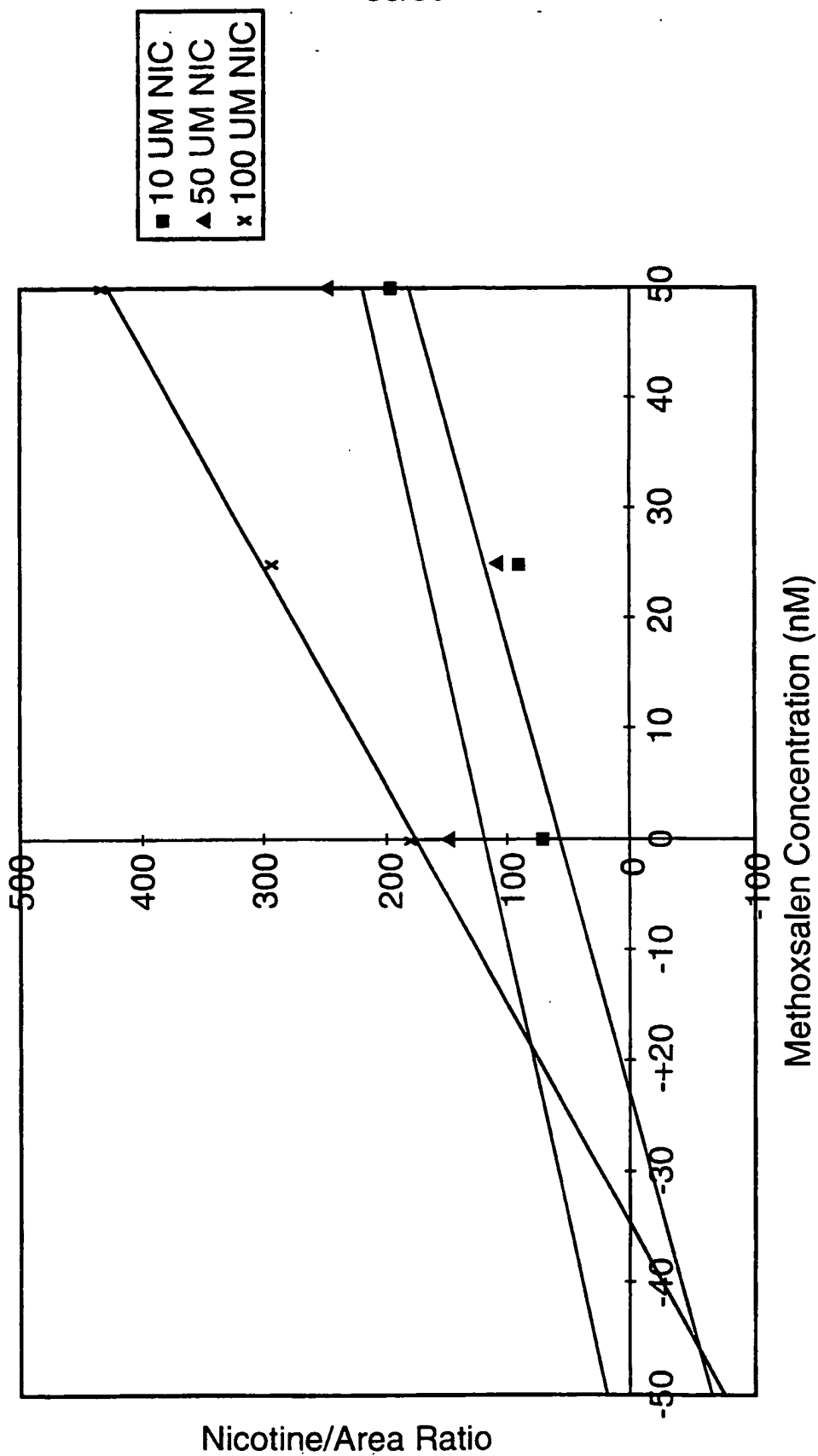


FIG.32

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Cornish-Bowden Plot of Methoxsalen Inhibition of Nicotine to Cotinine Formation
with 10 Minute Pre-incubation in K28 Human Liver Microsomes



Methoxsalen Concentration (nM)

FIG.33

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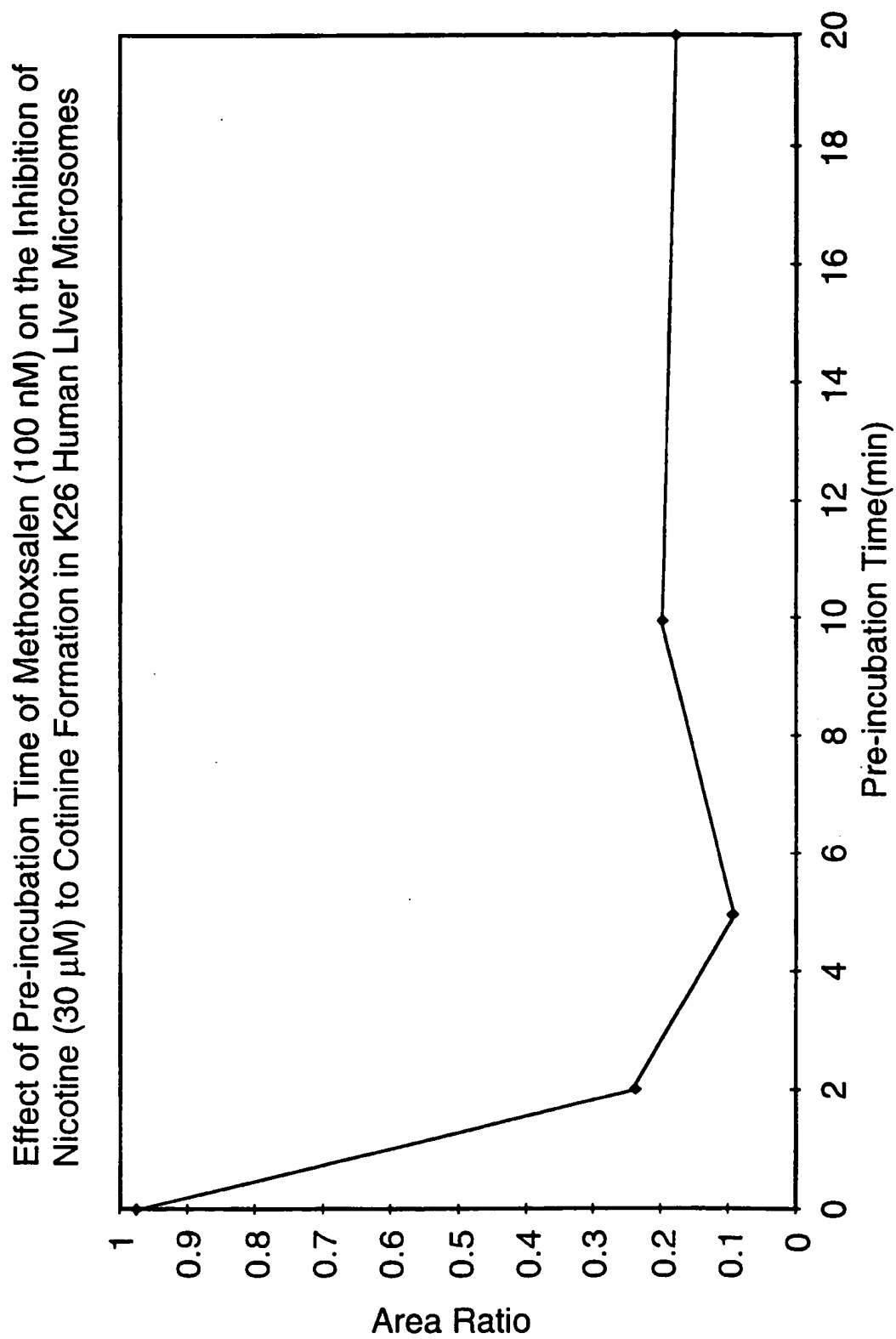


FIG.34

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Dixon Plot of Naringenin Inhibition of Nicotine to Cotine Formation with 10 minute
Preincubation in K26 Human Liver Microsomes

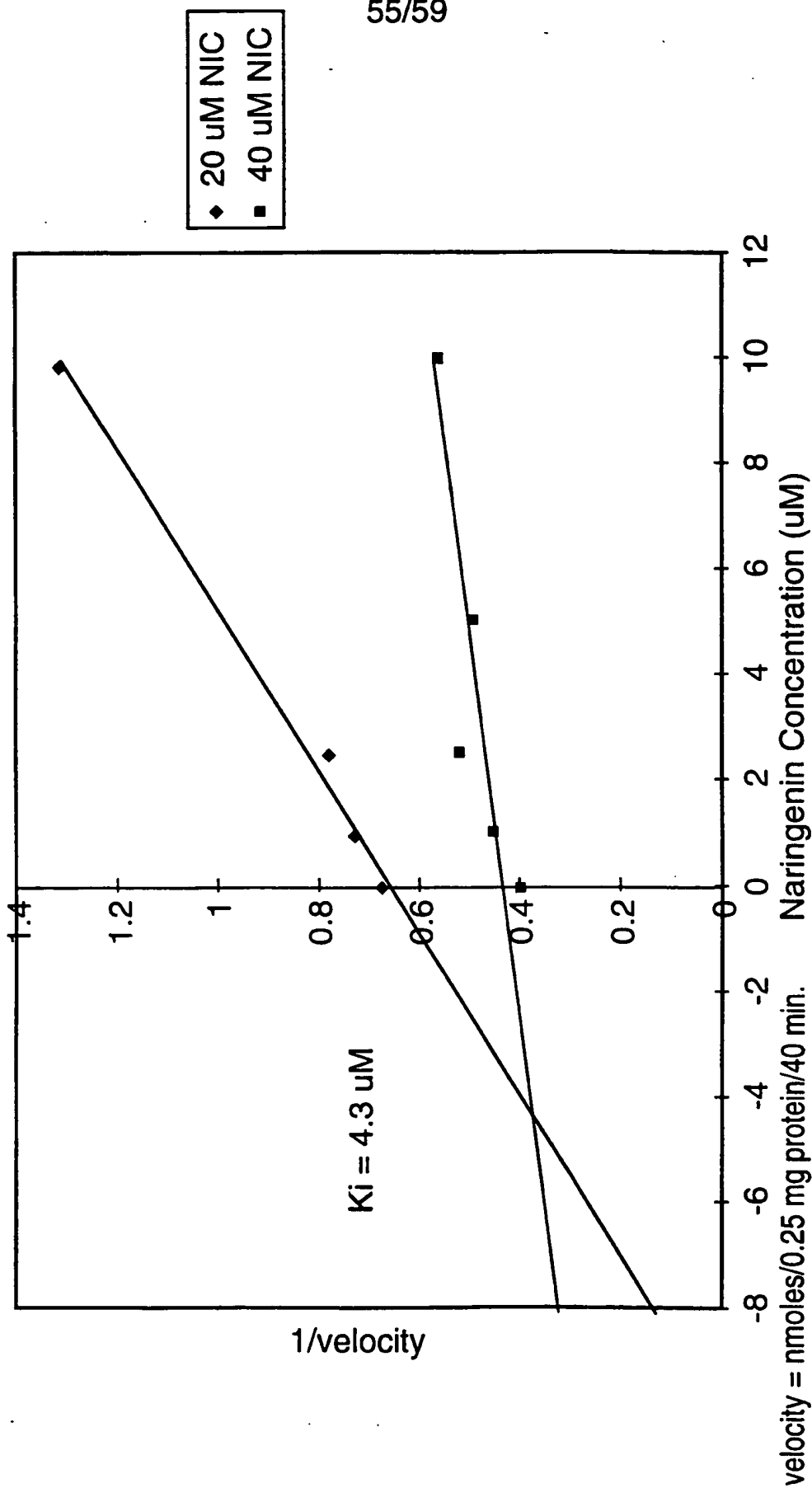


FIG.35

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Dixon Plot of Diethyldithiocarbamic Acid Inhibition of Nicotine to Cotinine Formation with 10 Minute Preincubation in K26 Human Liver Microsomes

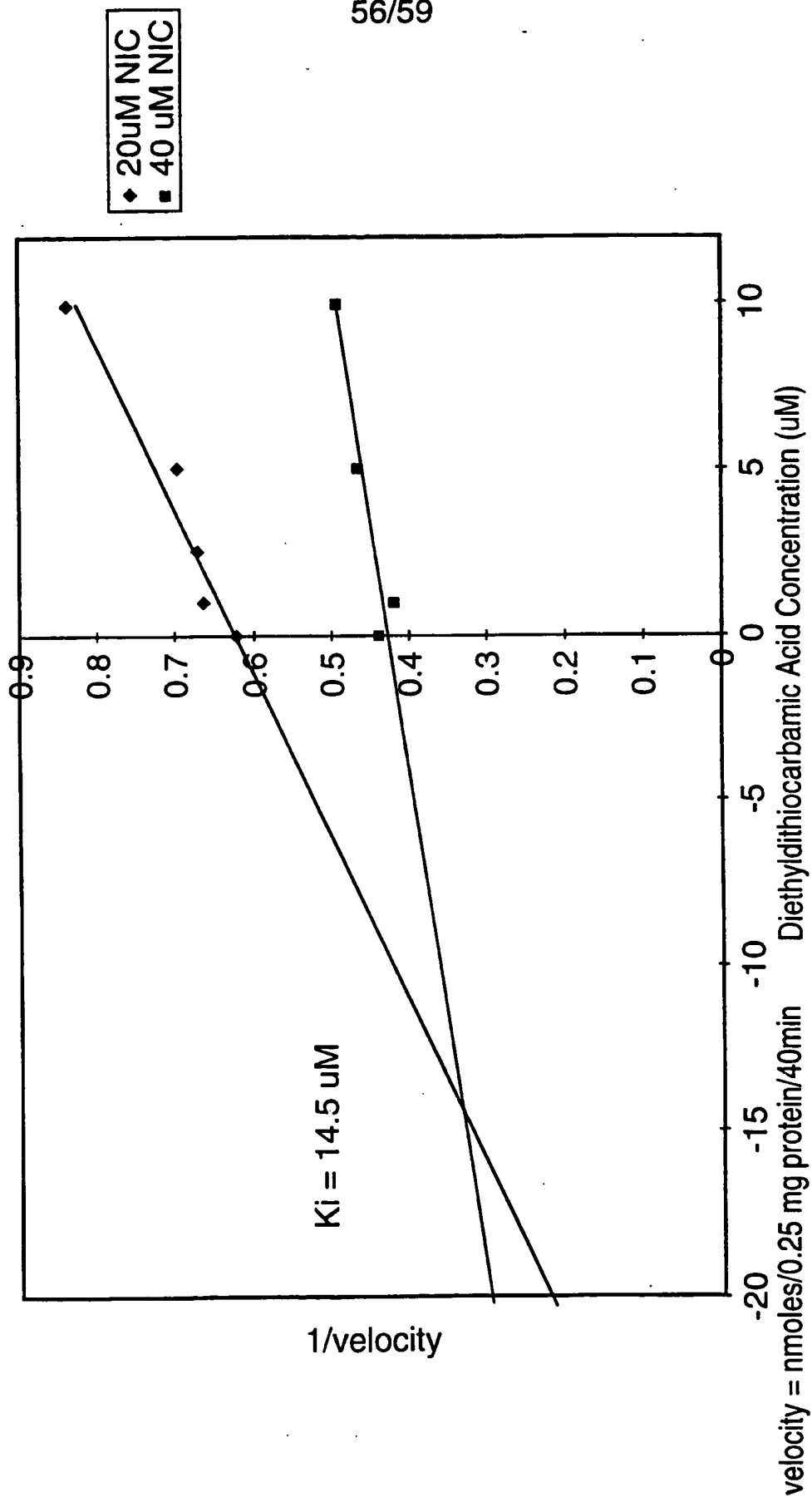


FIG.36

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Comparision Between Morning and Afternoon Testing Sessions

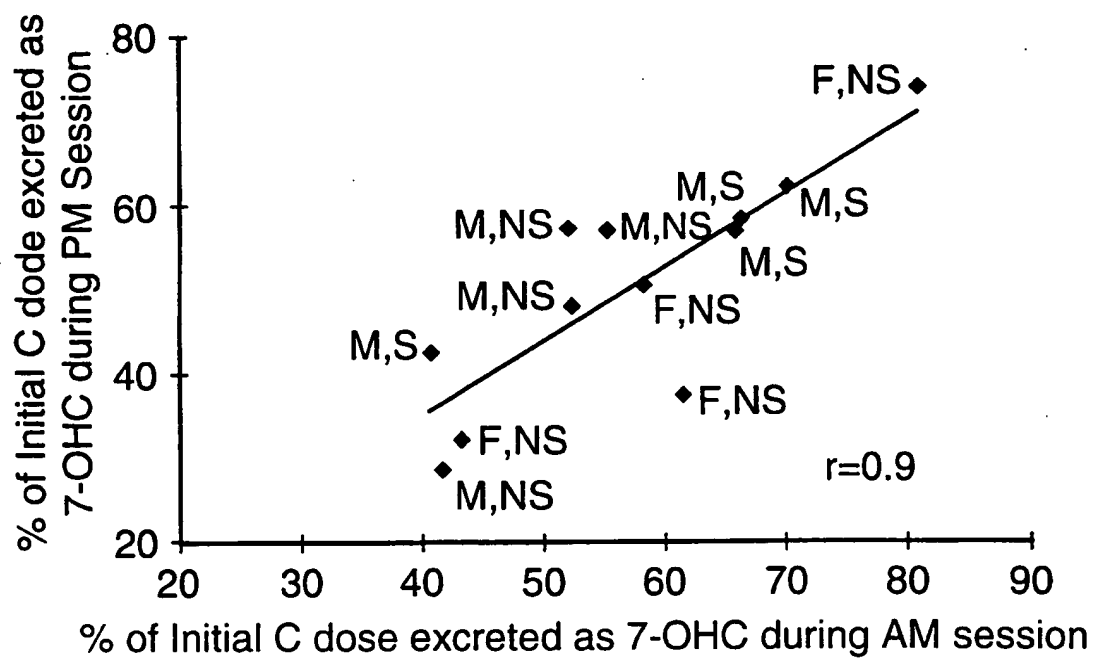
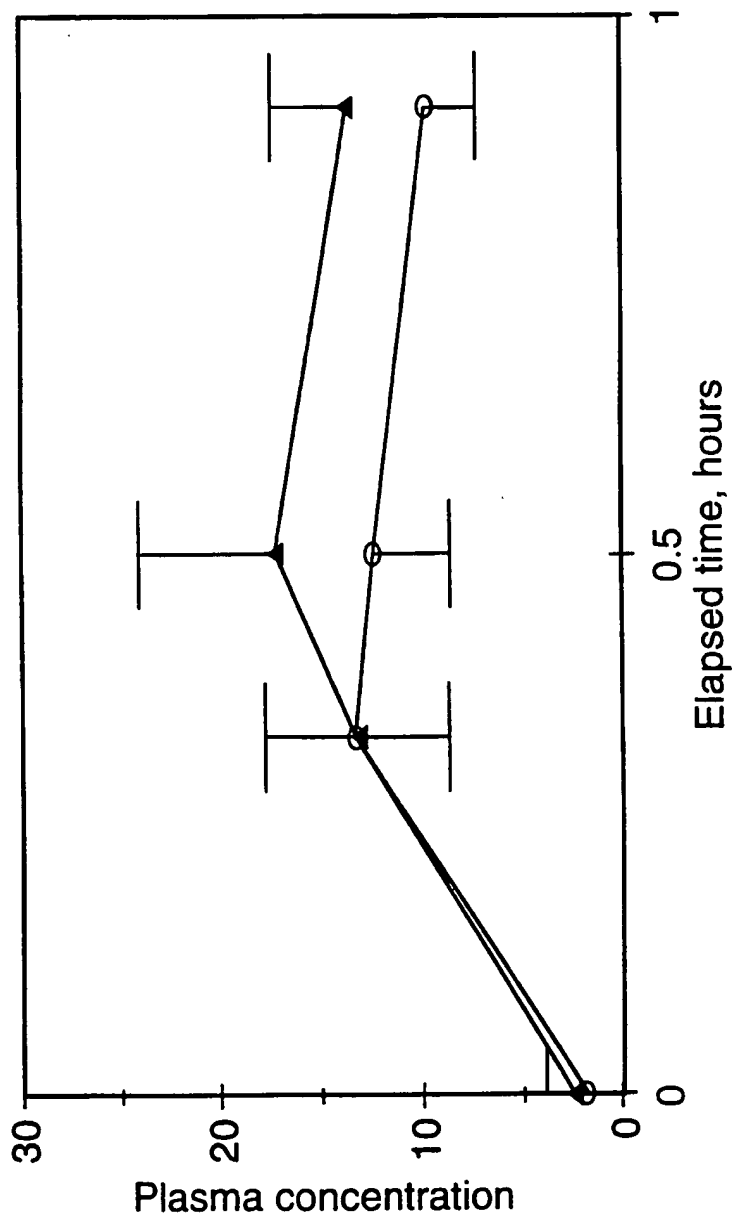


FIG.37

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Metabolism of Nicotine over one hour
Mean and s.d., seven subjects



—○— Placebo, AUC=12 —▲— Methoxsalen, AUC=15
Placebo vs Methoxsalen AUC to 1 hour:
 $F(1,6)=8.07, p=0.0295$

FIG.38

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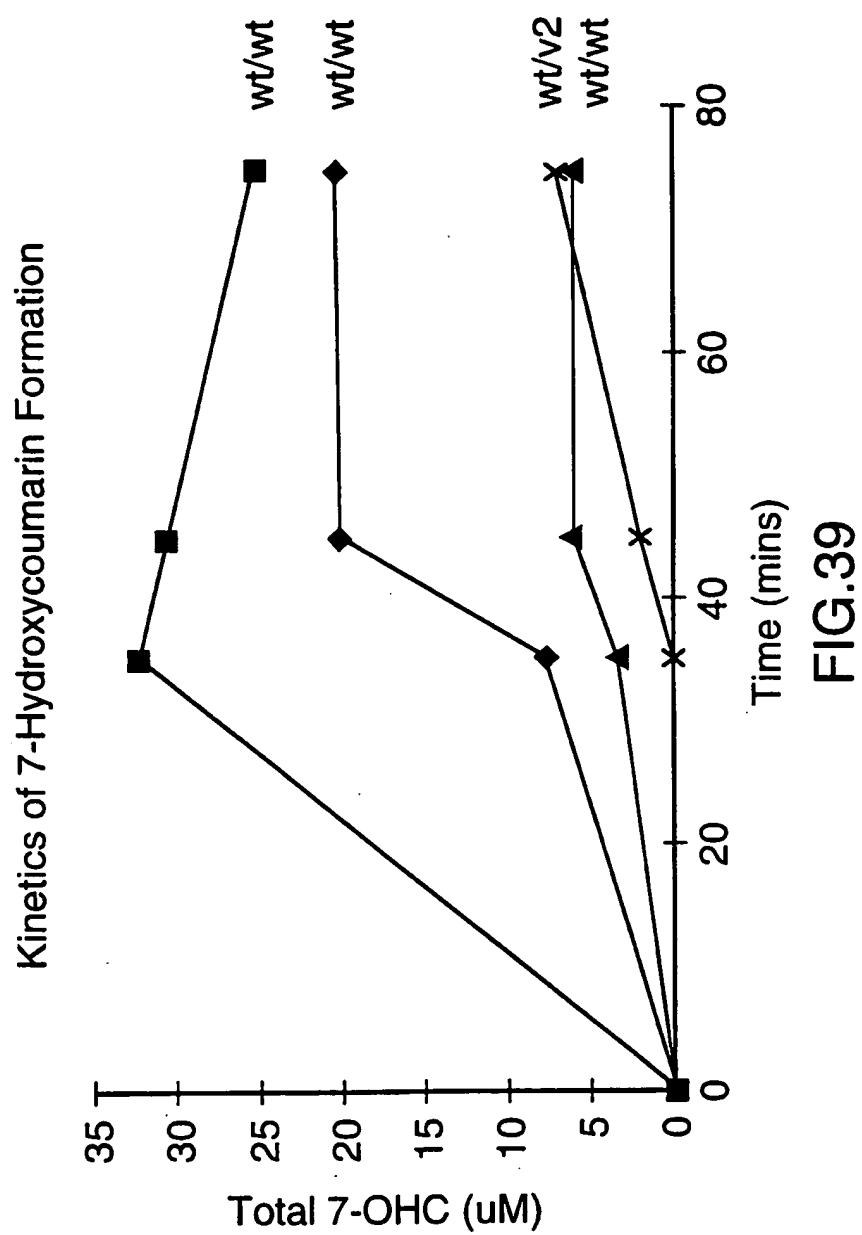


FIG.39